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The effects of adding a neuromuscular electrical stimulation device to a progressive resistance training programme in people with multiple sclerosis

Item Type	Thesis
Authors	Hughes, Lonan
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UNIVERSITY of LIMERICK
O L L S C O I L L U I M N I G H

**The Effects of Adding a Neuromuscular Electrical
Stimulation Device to a Progressive Resistance Training
Programme in People with Multiple Sclerosis**

A thesis in the fulfilment of the requirements for the degree of
Master of Science

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Submitted to the University of Limerick, April 2011

Abstract

Title: The Effects of Adding a Neuromuscular Electrical Stimulation Device to a Progressive Resistance Training Programme in People with Multiple Sclerosis

Author: Lonán Hughes

Background: Multiple Sclerosis (MS) is a progressive demyelinating disease of the central nervous system. It is recognised that people with MS (PwMS) who require a mobility aid, experience higher levels of disability, compared to those without mobility impairment. Decreased strength of the lower limbs is a primary problem, which is clinically associated with functional limitations in MS. Progressive resistance training (PRT) and neuromuscular electrical stimulation (NMES), to a lesser degree, are effective rehabilitation strategies to improve strength and function in PwMS. Presently, there is limited literature to support superimposing NMES on PRT in PwMS, particularly in the home-setting. The clinical profile literature of PwMS who use a walking aid, is also limited.

Aims: The primary aim of this thesis was to investigate the effects of adding an NMES device (Kneehab) to a home-based PRT in PwMS who use a walking aid. Secondary aims included, evaluating the clinical profile of this population and determining participant satisfaction with the Kneehab device.

Methods: The study used a randomised design to compare 12 weeks of home-based PRT to the same with superimposed NMES. The Kneehab device is designed for the quadriceps. The study assessor was blinded to group allocation. Participants were evaluated at week 0, 6 and 12 for a number of important clinical problems that were identified in the literature review. These included quadriceps strength (primary outcome), quadriceps thickness and endurance, spasticity, balance, mobility, health-related quality of life (HRQoL) and fatigue. Participants in the Kneehab group completed a device satisfaction questionnaire.

Results: Thirty-seven PwMS participated in the study. The baseline data for this group showed that muscle weakness, balance and mobility limitations were severe problems. Moderate correlations between quadriceps endurance and balance ($r=0.692$), and quadriceps endurance and mobility ($r=-0.583$) were shown. Twenty-five participants completed the study (PRT $n=10$; Kneehab $n=15$). Two-drop-outs in the Kneehab group were due to muscle spasm induced by the device. In both groups, quadriceps strength increased non-significantly while balance and gluteal strength improved significantly ($p<0.05$). The Kneehab group improved significantly on plantar-flexion strength, rectus femoris thickness, quadriceps endurance, perceived spasticity, HRQoL and fatigue (all $p<0.05$). The plantar-flexion strength, spasticity, HRQoL and fatigue improvements in the Kneehab group were significantly greater than the PRT group (all $p<0.05$). The Kneehab group also completed significantly more sessions, and total and quadriceps work (all $p<0.05$). Participants were satisfied with the usability and value of having the Kneehab device.

Conclusion: This preliminary research indicates that adding an NMES device to a PRT programme for PwMS who use a walking aid results in better outcomes than PRT alone. This may be due to a placebo type effect, whereby participants were motivated to complete a more exercise due to having the device. Recommendations for future research to determine the effects of this superimposing NMES on PRT are made.

Declaration

I declare that this thesis is entirely my own work and that it has not been submitted as an exercise for a degree at this or any other University.

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Acknowledgements

I would like to extend my gratitude to my supervisors, Dr. Susan Coote and Professor Alan Donnelly, who provided excellent guidance, wisdom, support and encouragement throughout this project.

I would also like to thank Mr. Gary Rainsford and Mr. Conor Minogue for their contributions to designing and undertaking the study.

To BMR Ltd. and the Irish Research Council for Science Engineering and Technology, for their generous financial support, without which, this project would not have been possible.

I would also like to thank:

- The staff in the MS Society of Ireland for their assistance with recruitment, particularly, Angela Minogue, Carol McKenzie, Aidan Larkin and Matti Twomey.
- All the staff in the Physiotherapy Department in the University of Limerick for their superb support and advice throughout my time in UL.
- Dr. Jean Saunders for her advice on all matters statistical.
- My fellow post-graduates; Maria, Neasa, Catriona, Marie, Laura, Derek and Elaine for the helpful academic and social conversations that kept me going!

A special and sincere thanks to all participants who volunteered their time and effort, without which this project would not have been feasible.

Many thanks to Dr. Aisling O'Donnell for her thorough proof reading and constant support throughout.

Finally, to my family and friends, in particular my mother, Sally, thank you for all the endless support, encouragement, understanding and patience throughout my time in university.

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List of Abbreviations

μs – microsecond

Ω – Volts

ACSM – American College of Sports Medicine

ADL – Activities of Daily Living

ANOVA – Analysis of Variance

BBS – Berg Balance Scale

CI – Confidence Interval

CID – Clinically Important Difference

CKC – Closed Kinetic Chain

cm – Centimetre

CNS – Central Nervous System

CSA – Cross-Sectional Area

CT – Computed Tomography

DOMS – Delayed Onset Muscle Soreness

EDSS – Expanded Disability Status Scale

FS – Functional System

GNDS – Guys Neurological Disability Scale

HHD – Hand-Held Dynamometer

HRQoL – Health Related Quality of Life

Hz – Frequency

ICC – Intra-Class Correlation

ICF – International Classification of Functioning, Disability and Health

IKD – Isokinetic Dynamometry

IQR – Interquartile Range

mA – Milliamps

MAS – Modified Ashworth Scale

MFIS – Modified Fatigue Impact Scale

m – metre

mm – Millimetre

MRI – Magnetic Resonance Imaging

MS – Multiple Sclerosis

MSIS-29 – Multiple Sclerosis Impact Scale-29

MSSI – Multiple Sclerosis Society of Ireland
MSWS-12 – Multiple Sclerosis Walking Scale-12
N- Newtons
NARCOMS - North American Research Committee on Multiple Sclerosis
NMES – Neuromuscular Electrical Stimulation
OKC – Open Kinetic Chain
PRT – Progressive Resistance Training
PASW - Predictive Analytics SoftWare
PCC – Pearsons Correlation Coefficient
PwMS – People with Multiple Sclerosis
QoL – Quality of Life
RCT – Randomized Controlled Trial
RF – Rectus Femoris
RM – Repetition Maximum
RoI – Republic of Ireland
RTUS – Real-Time Ultrasound
SCC – Spearmans Correlation Coefficient
SPSS – Statistical Package for Social Sciences
STS – Sit-to-Stand
TUG – Timed Up and Go test
VAS – Visual Analogue Scale
VI – Vastus Intermedius
VL – Vastus Lateralis
VM – Vastus Medialis
WHO – World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Background

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune disease causing demyelination of the central nervous system (CNS) (Noseworthy et al. 2000). The symptoms and clinical problems experienced by people with MS (PwMS) are diverse and impact upon their quality of life (QoL) (Khan et al. 2006, Wu et al. 2007) and activities of daily living (ADL) (Einarsson et al. 2006, Mansson and Lexell 2004). Globally, the prevalence of MS is estimated at 30 per 100,00 and is on the rise (World Health Organization 2008). In the Republic of Ireland, the most recent survey estimates a prevalence of 120-184 per 100,000 (McGuigan et al. 2004), which is substantially higher than the international average. The economic implications of an increasing prevalence of MS were highlighted in a recent systematic review (Naci et al. 2010), which indicated that cost of care increases with higher levels of disability. Consequently, interventions that are aimed at reducing disability were emphasised as important to alleviate the economic burden of MS.

Disability in the MS population is recognised as being highly variable (Confavreux et al. 2003, Lucchinetti et al. 2000). As a result, identifying sub-groups by disability level that are a priority for rehabilitation can be difficult. The Expanded Disability Status Scale (EDSS – **Appendix 1**) (Kurtzke 1983), which is the most widely used clinical tool for evaluating PwMS, utilises mobility status as a main criterion to categorise disability level. This approach of categorising disability level by mobility status is supported by the high prevalence of mobility impairments in the MS population (Wu et al. 2007), and the strong association in PwMS between greater mobility impairments and increasing disability (Salter et al. 2009). The implication is that PwMS who experience more restricted mobility are a priority for rehabilitation due to the greater personal and economic impact associated with their level of MS disability. According to recent reviews of the exercise rehabilitation literature for PwMS (Snook and Motl 2009, Dalgas et al. 2008, Rietberg et al. 2005) the

majority of studies have investigated the effects of exercise in people with a lower disability level on the EDSS (<5.5, no mobility aid required) and thus less mobility impairment. Therefore, the primary interest in this thesis is to build on the rehabilitation literature for PwMS who use a mobility aid.

In the primary care setting, individuals with MS have highlighted Physiotherapy as their number one need (MacLurg et al. 2005). In order to guide an effective rehabilitation service for PwMS who use a walking aid, profiling the clinically relevant problems of the population is important (Vazirinejad et al. 2008). A clinical profile can inform the level of impairments and relationships between these impairments, thereby indicating specific rehabilitation needs. A number of studies have documented the clinical profile of heterogeneous populations of PwMS (Coote et al. 2010, Ytterberg et al. 2008, Wu et al. 2007, Paltamaa et al. 2006, Khan et al. 2006, Minden et al. 2004). However, only Khan et al (2006) sub-grouped the clinical problems of their cohort by disability level. As a result, the implementation of an effective rehabilitation service that targets the most important and severe clinical problems experienced by sub-groups of PwMS, is restricted. To date, no study has exclusively investigated the clinical profile of PwMS who use a walking aid.

One of the primary impairments associated with the clinical profile of PwMS is lower limb muscle weakness (Schwid et al. 1999, Lambert et al. 2001). This impairment has been shown to present unilaterally (Chung et al. 2008), which is consistent with the clinical presentation of MS impairments. For PwMS who use a walking aid, strength deficits are a substantial problem. This assertion is supported by their need for a mobility device and the fact that muscle weakness has been shown to increase with disability level on the EDSS (Ponichtera et al. 1992). Clinically, muscle strength, particularly of the quadriceps, is acknowledged as important in performing functional activities in PwMS. However, in the MS literature, the only relationship established between leg strength and function is between quadriceps strength and gait speed (Thoumie et al. 2005, de Souza-Teixeira et al. 2009). In the older adult and stroke populations, associations between quadriceps strength and functional tasks have been demonstrated (Skelton et al. 1994, Moxley Scarborough et al. 1999,

Kobayashi et al. 2011). Therefore, considering the strength deficits of PwMS who use a walking aid, a programme of quadriceps strengthening may benefit their functional capacity. Improvements in function and subsequently disability are associated with reduced cost of care (Kobelt et al. 2006) and enhanced QoL (Wu et al. 2007).

Progressive resistance training (PRT) is an established rehabilitation option for increasing muscle strength in PwMS (Dalgas et al. 2008). A recent systematic review indicated that neuromuscular electrical stimulation (NMES) results in modest strength gains in the stroke population (Glinsky et al. 2007). However, translation of strength increases to functional improvements remains limited with PRT and NMES. Glinsky et al (2007) recommended combining NMES and PRT to increase strength gains. Physiologically, this rationale is supported by the fact that individuals with MS have been shown to be unable to fully activate their muscles (Rice et al. 1992, Sharma et al. 1995, Ng et al. 2004), while electrical stimulation has been shown to increase muscle activation (Adams et al. 1993) and neural drive to the muscle (Gondin et al. 2006, Vanderthommen and Duchateau 2007). Therefore, superimposing NMES on voluntary muscle contraction may achieve a greater strength increases than voluntary contraction alone, due to an effect on the neural component of strengthening. Considering the time frame for central (neural) adaptations to strength training, this effect would be expected in the initial stages of training (Gabriel et al. 2006). In order to achieve the peripheral (hypertrophy) effects, a training programme of longer than 8 weeks (Staron et al. 1994, Hickson et al. 1994, Akima et al. 1999), will be necessary.

The use of strengthening exercises that involve functional movement has been recognised as an important factor in achieving functional carryover through motor learning (Carroll et al. 2001). This assertion is based on the principles of neuroplasticity, whereby function can be improved through task based practice (Ploughman 2002). A previous study of people with stroke demonstrated enhanced neuroplastic changes and improved functional performance, when triggered NMES was superimposed upon voluntary contraction compared to voluntary contraction alone (Kimberley et al. 2004). Therefore, although

superimposing NMES on a PRT programme is a novel approach to strengthening in PwMS, theoretically the evidence supports potential strength and functional gains.

The use of assistive technology such as NMES devices to improve functional capabilities in PwMS has been recommended previously (Blake and Bodine 2002). Considering the increasing prevalence of MS, potential additional therapeutic benefits achieved by supplementing a PRT programme with an NMES device may be important in reducing the economic costs of rehabilitation. Furthermore, with the ongoing shift in health care delivery in the Republic of Ireland towards the internationally used primary care model (Department of Health and Children 2001), the use of NMES devices allows for therapy to be undertaken by the person in the home setting. In order to ensure that the device is suitable for the population, the evaluation of user satisfaction, particularly in terms of usability, is recommended (Lehoux 2004).

1.2 Thesis Aims

The primary aim of this thesis was to undertake a pilot study to evaluate the effects of adding an NMES device to a home based PRT programme for PwMS who use a walking aid.

The secondary aims are to:

1. To review the clinical profile, PRT and NMES literature for PwMS who use a walking aid.
2. To investigate the clinical profile of PwMS who use a walking aid.
3. To investigate participants' satisfaction with the usability of the NMES device.

CHAPTER 2 – A REVIEW OF THE LITERATURE

2.1 Introduction

In this chapter, the MS literature in two areas is reviewed. First, a narrative overview will be provided on the clinical profile of PwMS, including the main clinical problems experienced and the relationships between these problems. The second part and main focus of the chapter will review and discuss the PRT and NMES literature for PwMS who use a walking aid, with a view to developing a protocol for combining the interventions.

2.2 Part One - Clinical Profile of PwMS

A clinical profile in the physiotherapy context consists of the main clinical problems a population experiences and associations between these problems. In the MS population the clinical problems experienced are numerous and varied both in prevalence and severity of presentation. Consequently, in order to describe the complex presentation of PwMS in a standardized manner, the International Classification of Functioning, Disability and Health (ICF) framework (World Health Organization 2001), has been recommended for the MS population (Kesselring et al. 2008). Recently, the ICF framework was found to adequately describe the functioning and disability of PwMS (Holper et al. 2010). As a result the ICF domains of body functions and structure, activities, and participation can be used to classify the clinical problems experienced by PwMS. The body functions and structure domain refers to impairments in a physiological system or an anatomical part, the activity domain relates to limitations in the execution of a task or action, and the participation domain describes restrictions in involvement in a life situation (Dahl 2002).

The interaction between the clinical problems in these domains is the second consideration in the clinical profile. An understanding of the relationships between clinical problems is important as it can assist clinicians with identifying

causes of deterioration in function or disability, and it may provide guidance on appropriate rehabilitation approaches to improve related problems simultaneously. In previous studies in the older adult and stroke populations, the importance of strength to functional performance has been demonstrated (Moxley Scarborough et al. 1999, Bean et al. 2002, Weiss et al. 2000, Kobayashi et al. 2011). Therefore, the relationship between muscle strength and functional activities is the primary interest in this review of relationships between clinical problems in PwMS.

2.2.1 Aim and Objectives

The aim in the first part of this chapter is to provide a narrative overview of the clinical profile of PwMS. The specific objectives are to:

1. Outline the most prevalent and important clinical problems for PwMS.
2. Identify the established relationships between these problems in PwMS and other neurological populations.

2.2.2 Clinical Problems in PwMS

Body Functions and Structures Domain

In three studies including PwMS with a wide range of disability on the Expanded Disability Status Scale (EDSS), muscle weakness of the lower limbs was a commonly reported problem (Coote et al. 2010, Paltamaa et al. 2006, Holper et al. 2010). Compared to healthy age-matched controls, strength deficits of between 11% and 54% have been recorded in the MS population (Carroll et al. 2005, de Haan et al. 2000). Considering the strong relationship between muscle strength and muscle cross-sectional area (CSA) in the health population (Huygens et al. 2004, Sipila et al. 2004), and PwMS (Kent-Braun et al. 1997, Ng et al. 2004), muscle atrophy is also an important impairment in PwMS. Presently, there is conflicting evidence regarding the severity of muscle atrophy in PwMS. Two studies have demonstrated no difference in muscle CSA for the tibialis anterior and vastus lateralis, compared to healthy age-matched controls, when measured with magnetic resonance imaging (MRI) and muscle biopsies respectively (Ng et al. 2004, Carroll et al. 2005). However, in a more mobility impaired population of PwMS, tibialis anterior CSA was shown to be 32%

smaller than matched controls (Kent-Braun et al. 1997). This suggests that muscle atrophy, similar to muscle weakness, is a more substantial impairment in more disabled PwMS. The disability level of PwMS who use a walking aid suggests that muscle atrophy is likely to be a relevant problem for the population of interest in this thesis.

Reduced muscular endurance is a further muscle impairment in PwMS, which has not been widely reported in the clinical profile literature. Recently, impaired muscular endurance was reported as a cause of accidental falls by PwMS (Nilsagård et al. 2009a). In a comparison with matched controls, two cohorts of PwMS with a wide range of disability on the EDSS (2-8) demonstrated significantly reduced muscular endurance of the quadriceps and tibialis anterior (de Haan et al. 2000, Sharma et al. 1995). This suggests that decreased muscle endurance is a problem for PwMS with varying levels of disability. The well recognised reduced levels of physical activity in PwMS (Motl et al. 2005), supports this view that impaired muscular endurance is a prevalent and under-reported problem for PwMS.

Compared to impaired muscle endurance, spasticity is a problem in PwMS, which is well documented in the literature. Based on the registry of over 20,000 PwMS from the North American Research Committee on MS (NARCOMS), spasticity is a highly prevalent problem, with 84% of the cohort reporting symptoms in their lower limbs (Rizzo et al. 2004). A further finding of the Rizzo et al. (2004) profiling study was that PwMS who experienced greater mobility impairment had more severe spasticity. Therefore, it can be expected that the population of interest in this thesis are likely to experience spasticity.

Activity Domain

In a large population-based study of PwMS (n=2,109), with a diverse range of disability based on disease type and duration of illness, difficulty walking was the second most common problem reported, with 67% of participants experiencing limitations (Wu et al. 2007). This finding of a high prevalence of mobility impairment is consistent with reports in other cohorts of 68 – 79% (Coote et al. 2010, Khan et al. 2006).

Another important daily activity that PwMS experience limitations with is balance. Difficulties with balance was the main problem reported most frequently (18%) by an Irish cohort of PwMS (Coote et al. 2010). Similarly, 29% of people in another study considered balance to be one of the main 3 symptoms impacting their daily lives (Paltamaa et al. 2006).

Participation Domain

Restrictions in QoL are highly prevalent in the MS population, with 71% of participants in a population-based study (n=2,156), reporting this as an issue (Minden et al. 2004). Compared to healthy controls and other chronically impaired populations, PwMS experience significantly greater reductions in QoL (Wu et al. 2007). The impact of a lower QoL in PwMS is substantial, as strong associations have been demonstrated between low QoL and reduced independence in daily activities and physical activity (Wu et al. 2007, Motl et al. 2005).

Fatigue is another symptom that PwMS experience, which restricts participation. Individuals with MS have reported fatigue as the most common problem affecting their daily activities (Paltamaa et al. 2006). The debilitating effects of fatigue have been highlighted by its relationship with disability level, depression and mood (Kroencke et al. 2000). In addition, fatigue is a highly prevalent problem in the MS population, with prevalence estimates ranging from 70 – 83% (Vazirinejad et al. 2008, Wu et al. 2007).

2.2.3 Relationships between Clinical Problems in PwMS

Based on the main clinical problems for PwMS identified in the previous section, this section will provide a narrative of the relationships that have been established between these problems in the MS and other relevant populations, with a particular focus on the role of muscle strength and endurance on function.

Balance and Muscle Strength, Muscle Endurance and Spasticity

Impaired balance is recognised as one of the primary risk factors associated with the high incidence of falls in the MS population (Finlayson et al. 2006). Decreased muscle strength may be a causative factor, as a recent systematic review found that in 84% of studies in the older adult population there was a significant association between strength and balance (Orr 2010). Similarly, significant associations between quadriceps strength and both static and dynamic balance have been demonstrated in a stroke population (Kobayashi et al. 2011). The relationship between balance and quadriceps strength has been investigated most frequently (Carter et al. 2002, Kligyt et al. 2003). Only one study, in the older adult population, has evaluated the relationship between balance and the strength of the other lower limb extensors (gluteals and plantar-flexors) (Binda et al. 2003). Significant associations between balance and extensor strength were demonstrated. In PwMS, these relationships have not been investigated to date, despite the well-acknowledged impairment of strength and balance.

Similarly, the association between muscular endurance and balance has not been investigated in the MS population, despite PwMS reporting that muscular endurance is one of the factors they perceive to be related to falls (Nilsagård et al. 2009a). A review of the studies investigating the influence of endurance training on falls incidence in older adults found a positive effect (Carter et al. 2001). Therefore, an indirect relationship between muscular endurance and balance is implied, which may be important in PwMS.

Lower limb spasticity is another clinical problem that has been identified by PwMS as a cause for experiencing a fall (Nilsagård et al. 2009a). This was substantiated by the finding that spasticity is predictive of fallers in MS (Nilsagård et al. 2009b). Considering this relationship, an association between spasticity and balance may exist. However, this has not been evaluated in the MS population.

The clinical implication of establishing whether relationships exist between balance and the problems of impaired muscle strength, muscle endurance and

spasticity, is that rehabilitation strategies that improve these problems may also have a complementary effect of reducing balance limitations.

Mobility and Muscle Strength, Muscle Endurance and Spasticity

In recent years, the relationship between mobility and strength has been investigated in the MS population (Mevellec et al. 2003, Thoumie et al. 2005, de Souza-Teixeira et al. 2009). These studies found that with increasing quadriceps strength, gait speed increased. However, the relationship between the strength of all the extensor muscles (which provide propulsion during gait) and gait speed has not been investigated in PwMS.

In a similar manner, the influence of muscular endurance on mobility limitations in PwMS has not been previously evaluated. A relationship may exist between these problems, as the distance of 284 metres (m) covered by PwMS on the 6 minute walking test (Gijbels et al. 2010), is substantially less than the mean distance of 603 – 659 m completed by healthy older adults (Camarri et al. 2006, Bautmans et al. 2004). A possible explanation for this difference is reduced muscular endurance.

The impact of spasticity on gait in neurological populations is widely recognised (Krawetz and Nance 1996, Waters and Mulroy 1999). Rizzo et al. (2004) demonstrated a relationship between spasticity and mobility level. This relationship is supported by the clinical reports of concurrent disability between lower limb spasticity and mobility (Beard et al. 2003). Similarly, a recent systematic review (Lakhan and Rowland 2009) found that pharmacological treatment with cannabis improved spasticity in PwMS with a trend for improvements in mobility. Therefore, there is a strong indication that a relationship exists between these clinical problems.

Addressing these current gaps in the MS literature is important clinically, in terms of identifying the impairments in body functions and structures that have an impact on mobility limitations in PwMS. By establishing whether impaired muscle strength, muscle endurance and spasticity are associated with mobility,

appropriate rehabilitation strategies to improve mobility in PwMS can be identified.

Muscle Endurance and Fatigue

Muscular endurance is the ability of a muscle to continue to contract for a prolonged period until fatigue. Therefore, a relationship between fatigue and muscular endurance may be implied. This relationship was investigated in PwMS using grip strength as the muscular variable (Iriarte and Castro 1998). A relationship was not demonstrated, which is to be expected as upper limb impairments and strength loss are less common compared to the lower limb (Schwid et al. 1999). Consequently, the impact of symptomatic fatigue on muscular endurance of the lower limbs and vice versa in MS remains unknown.

Muscle Strength and Thickness

Muscle weakness and atrophy are common problems for PwMS. Although it is well established in the literature for the healthy population that muscle CSA is the prime determinant for strength (Huygens et al. 2004), the research in the MS population is less strong. To date, two studies have demonstrated that a relationship exists between strength and muscle size in the tibialis anterior, in PwMS (Kent-Braun et al. 1997, Ng et al. 2004). Establishing whether a relationship exists between these variables in other muscles, in PwMS, is important to substantiate the results of Kent-Braun et al. (1997) and Ng et al. (2004). In addition, it will support the assertion that strengthening increases muscle size in PwMS, resulting in more sustained strength benefits.

2.2.4 Conclusion on Clinical Profile of PwMS

The clinical profile literature for PwMS suggests that individuals with MS experience a diverse range of problems that affect their ability to complete daily activities. The main limitation in this literature is the heterogeneous level of disability of the populations included. As a result, refined clinical profiles of specific populations, such as those who use a mobility aid, are not available. The clinical implication is that rehabilitation service planning is limited as the severity of problems in sub-groups of PwMS is unknown. A similar issue exists

in the literature investigating relationships between clinical problems in PwMS. Although relationships have been demonstrated in other neurological and geriatric populations, in the MS population this research is limited. Consequently, the influence of clinical problems on one another is not understood. As a result designing targeted rehabilitation programmes is limited.

2.3 Part Two – PRT and NMES Literature

In addressing the clinical problems experienced by PwMS, a review by Dalgas et al. (2008) demonstrated that PRT has beneficial effects, especially for strength. However, the majority of the studies in that review included PwMS who did not require a walking aid. As a consequence the benefits of PRT for PwMS who experience a higher level of disability are unclear. The use of NMES in the rehabilitation of PwMS and other neurological conditions, has also shown improvements in clinical problems, particularly strength (Glinsky et al. 2007, Ada et al. 2006). In their review of the literature, Glinsky et al. (2007) recommended superimposing NMES on a strengthening programme as a direction for future research. Considering the superior strength, function and neuroplastic improvements shown with superimposing NMES on voluntary contraction compared to voluntary contraction alone in people with a stroke (Kimberley et al. 2004), this approach may also be beneficial for PwMS. To date, the literature investigating the effects of combining PRT and NMES in PwMS is limited.

2.3.1 Aim and Objectives

The aim of this part of the chapter is to review the PRT and NMES literature for PwMS who use a walking aid. The objectives are to:

1. Identify the primary clinical problems improved by PRT and NMES.
2. Evaluate the quality of the PRT and NMES literature for this population.
3. Determine a best practice protocol for combining PRT and NMES in a home based intervention, aimed at improving the main clinical problems.

2.3.2 Literature Review Methods

Literature Search

In order to develop a best practice protocol for combined PRT and NMES in PwMS, two systematic searches of the respective literature were completed. The Cochrane Handbook for Systematic Reviews of Intervention (Higgins and Green 2008), was used to inform the search strategy, appropriate search terms and selection criteria for the studies.

The databases searched were: Academic Search Complete, AMED, Biomedical Reference Collection, CINAHL, the Cochrane Library, Embase, Informaworld, Medline, Nursing and Allied Health Collection, Science Direct, SPORTDiscuss, Web of Knowledge and Wiley Interscience. For the PRT literature search, two search streams were necessary. The terms “Multiple Sclerosis” and “MS” were searched with:

1. “progressive resistance training”, “PRT”, OR “strength training”
2. “progressive resistance exercise” OR “strengthening exercise”

The search of the NMES literature used the terms “neuromuscular electrical stimulation” or “electrical stimulation” with “Multiple Sclerosis” and “MS”. For both searches only articles written in English and where a full text could be obtained were considered (i.e. conference abstracts were excluded).

Quality Assessment Tool

The Cochrane Collaboration’s tool for assessing the risk of bias (Higgins and Green 2008), was used to evaluate the methodological quality of the studies. This tool was selected as it addresses the main sources of methodological bias in six categories. The categories are: sequence generation; allocation concealment; blinding of participants, personnel and assessors; incomplete outcome data; selective outcome reporting; and other potential threats to validity. Three responses are possible for each category; “met” means there was no bias detected, “unmet” indicates there was a bias, and “unclear” indicates the description is inadequate to determine the risk of bias. The use of an “unclear” response, coupled with criteria for each category encouraging the assessor to use

their judgement in determining bias, allows for the quality of non-randomized controlled trials (non-RCT) to be assessed. Therefore, this tool was deemed more suitable with a number of the PRT and NMES articles using non-RCT designs.

2.3.3 PRT Inclusion/Exclusion Criteria

A total of 1,522 publications were returned for the PRT search. The title and abstracts of these publications were screened for the use of an MS population and a strengthening intervention. This resulted in 21 suitable articles. The reference lists of these articles were subsequently scanned and no additional articles were retrieved.

The 21 articles were examined in detail and were included in the review if:

- The study population of PwMS included individuals who used a walking aid (EDSS of 6 to 7.5 or stated walking aid use).
- A longitudinal design with a resistance training programme was used.
- The outcomes evaluated included any of the main clinical problems experienced by PwMS, as outlined above.

There were 8 articles that met the above criteria and were subsequently reviewed (**Table 1**). The articles that did not meet the criteria were excluded based on: the study population not including PwMS who use a walking aid (n=10) (Dalgas et al. 2010a, Dalgas et al. 2010b, Dalgas et al. 2009, Coco et al. 2007, Taylor et al. 2006, Gutierrez et al. 2005, Surakka et al. 2004, White et al. 2004), use of a non-resistance training intervention (n=2) (Çakit et al. 2010, Gehlsen et al. 1984), and the article being a review of the literature (n=1) (Dalgas et al. 2008).

2.3.4 PRT Literature Results

The quality of the 8 studies that met the inclusion criteria was generally poor, with only 2 studies (DeBolt and McCubbin 2004, Sabapathy et al. 2011), demonstrating a low level bias on the quality assessment tool (**Table 1**).

Table 1 PRT Literature

Study	Population	Study Design	Intervention					Main Findings (% Change)	Quality Score
			F	I	Type	T	D		
(Sabapathy et al. 2011)	n=21 Disease Steps Score 1-3 (3 = intermittent use of cane) All MS types	Randomized Cross-Over design, 8 week wash-out PRT vrs End. training Analysed n=16	2	Both: 3 – 5 Borg 2-3 x 6-10. PRT: Exercises & load progressed.	PRT: Upper & lower extremity muscles. End: Aerobic circuit – 8 stations	PRT: NR End: 65	8	Mobility (6MWT ; TUG) PRT= 8.7%* ; 9.3%* End= 3.9%* ; 6.9%* Fatigue (MFIS Physical Subscale); HRQoL (MSIS-29 Physical Subscale) PRT=9.2%* ; 10.3%* End=13.8%* ; 10.1%* Balance (FRT) PRT= 15.4%* End= 3.6%*	Met = 4 Unmet = 1 Unclear = 1 Bias = Low
(Fimland et al. 2010)	n=14 EDSS 2 – 6.5 All MS types	RCT PRT: n= 7 C: n= 7	5	4 x 4 at 85-90% 1 RM. Load progressed	PRT: Leg press & calf raises. Both: Aqua exs. & physiotherapy	Both: NR	3	Torque (MVC Plantar-flexors Nm) PRT = 14.8%* C = 3.4%	Met = 2 Unmet = 1 Unclear = 3 Bias = Moderate
(Filipi et al. 2010)	n=33 EDSS 1-6.5 RR, PP & SP MS	Single group pre-mid-post PRT & balance exs.	2	2-3 x 10. Load progression	PRT of trunk, upper & lower extremity muscles.	50	26	Fatigue (MFIS Physical Subscale) Week 0-13; 0-26: 26%* ; 24.2%* Mobility (T25FW) Week 0-13; 0-26: 1.6% ; 3.6%	Met = 0 Unmet = 6 Unclear = 0 Bias = High
(de Souza-Teixeira et al. 2009)	n=13 EDSS 1-6 (3 using walking aids) All MS types	Single group – pre-post PRT Participants as self-controls.	2	3 x 10-15 at 40-70% of MVC. Progressed bi-weekly.	Quadriceps - Concentric & eccentric.	NR	8	Strength (MVC N); Torque (Nm); Power (W) PRT=14.4%* ; 14.2%* ; 47.7%* C=-0.5% ; 0.6% ; 0.8% Endurance (Knee Extension reps) PRT = 84.1%* C = 2.2% Mobility (TUG) PRT = 16.7%* C = 0%	Met = 3 Unmet = 3 Unclear = 0 Bias = Moderate

MS: Multiple Sclerosis; **EDSS:** Expanded Disability Status Scale; **PRT:** Progressive Resistance Training Programme; **End:** Endurance; **RCT:** Randomized Control Trial; **C:** Control; **F:** Frequency (days/week); **I:** Intensity; **3 x 6-10:** 3 sets by 6-10 reps; **T:** Time (minutes); **D:** Duration (weeks) **NR:** Not reported; **RM:** Repetition Max; **6MWT:** 6 Minute Walk Test; **TUG:** Timed Up & Go; **MFIS:** Modified Fatigue Impact Scale; **MSIS-29:** Multiple Sclerosis Impact Scale; **FRT:** Functional Reach Test; **MVC:** Maximal Voluntary Contraction; **Nm:** Newton metres; *: Significant Difference Within Group; - % **change:** outcome worse; **RR:** Relapsing Remitting; **PP:** Primary Progressive; **SP:** Secondary Progressive; **Exs:** Exercise; **T25FW:** Timed 25 Foot Walk; **N:** Newtons

Study	Population	Study Design	Intervention					Main Findings (% Change)	Quality Score
			F	I	Type	T	D		
(Ayán et al. 2007)	n=30 EDSS 1 – 6 (mean 1.5) SP MS only	Single group pre-post PRT with balance exs.	3	1-2 x 2-3 reps less than max. Individually progression	Calisthenic exs. trunk, upper & lower extremity.	60	6	Strength (<i>Medicine Ball Throw ; Vertical Jump – cms</i>) 15.6%* ; 7.8% Mobility (<i>9m Zig-Zag</i>) 17.4%* Endurance (<i>Repetitions</i>) 34.5 – 133.3%* Balance (<i>Flamingo Balance Test</i>) 19%	Met = 2 Unmet = 4 Unclear = 0 Bias: High
(DeBolt and McCubbin 2004)	n= 36 EDSS 1 – 6.5 All MS types	Stratified (by EDSS) RCT Home PRT: n= 19 C: n= 17	3	2-3 x 8-12 BW vests increased by 0.5 – 1.5% of BW bi-weekly.	5 lower limb exs	35 - 50	8	Leg Extensor Power (<i>W</i>)** PRT = 23.9%*, C = 6.4% Balance (<i>AP ; ML ; Velocity Sway</i>) PRT = 19.9% ; 18.8% ; -2.2% C = 6.4% ; 21.7% ; -6.3% Mobility (<i>TUG</i>) PRT = 18.9%, C = 0.1%	Met = 4 Unmet = 0 Unclear = 2 Bias = Low
(Harvey et al. 1999)	n=17 11 used walking aids RR MS only	3 arm RCT Home PRT: n=6 HEP: n=6 C: n=5	14	5 x 10 Ankle weight (kg) ability to complete 10 reps.	PRT: Leg extension. HEP: Stretching, balance, mobility exs., & aerobic	NR	8	Torque (<i>Quadriceps KgF</i>) PRT=47.3%, HEP=4.3%, C=15.3% Mobility (<i>10m ; 50m</i>) PRT = 9.6% ; 0.9%, HEP = 6.5% ; 2.5%, C = -7.4% ; -7.1% Chair Transfer (<i>Time</i>) PRT=23.1%*, HEP=4.8%, C=-2.3%	Met = 3 Unmet = 0 Unclear = 3 Bias = Moderate
(Svensson et al. 1994)	n=5 EDSS 2-7 MS type NR	Case study Series	2-3	3 x 5-15 up to 50% of 1RM	Hamstrings, hip muscles & some aquatic & balance exs.	NR	4-8	Peak Torque (<i>Hamstrings</i>) Increased in 3, decreased & unchanged in 1 Fatigue (<i>VAS</i>) All improved (23 – 40mm)	Met = 3 Unmet = 3 Unclear = 0 Bias = High

BW: Body Weight; **AP:** Anterior-posterior; **ML:** Medio-lateral; **HEP:** Home Exercise Programme; **Kg:** Kilogram; **m:** metres **VAS:** Visual Analogue Scale; **KgF:** Kilograms of Force **mm:** millimetres; **: Significant Difference Between Groups

Three of the studies employed a RCT design and one used a cross-over design. The remaining 4 studies did not have a control or other intervention group for comparison of the PRT outcomes. The sample sizes in all studies were small (n= 5 to 36). Statistical power was only reported in the DeBolt and McCubbin (2004) study, which had the largest sample. However, this study was still under-powered. The MS populations in all studies were heterogeneous in terms of type of MS and disability level. The EDSS ranged from 1 or 2 up to 6.5 indicating that all studies contained a mix of PwMS who did and did not use a walking aid. The results of these sub-groups were not reported, limiting the generalisability of the results for PwMS who use a walking aid.

The delivery of the PRT intervention was generally in a gym setting: however, in two studies participants completed the PRT programme in the home setting (Harvey et al. 1999, DeBolt and McCubbin 2004). Both studies supervised the programmes by regular telephone calls to participants. Regardless of setting, the PRT programmes were well tolerated, with no reports of adverse effects or drop-out due to the exercise. Strength was the most commonly evaluated outcome, being measured in 6 of the 8 studies. The method of strength measurement differed between the studies with the use of isometric strength, torque and power. As a result, comparing the PRT programmes to determine which protocol resulted in the best outcomes is limited.

The PRT parameters were inconsistent between the studies and are outlined in **Table 1**. In terms of strength and specifically torque, the Harvey et al. (1999) study demonstrated the highest gains, although these were statistically non-significant. The frequency of exercise was 14 times per week in the Harvey et al. (1999) study. In 6 of the other 7 studies an exercise frequency of 2-3 times a week was used and statistically significant improvements in outcomes including strength were evident. In all studies the intensity of the exercise varied, with a different method to determine this parameter. Harvey et al. (1999) used an intensity of 5 sets of 10 repetitions with an ankle weight, which was increased when 10 leg extensions could be completed with sufficient effort and without discomfort. In the majority of studies, 2-3 sets and 8-12 repetitions were used, which resulted in statistically significant improvements. The muscles and type

of exercises used varied between all studies. Three studies included non-PRT exercise with the PRT. The time to complete the programme was not reported in 5 of the studies and ranged from 35 – 60 minutes in the other studies. Eight weeks was the most common duration for the PRT programmes, which was also used by Harvey et al. (1999). Durations of 3 and 26 weeks were used in other studies (Fimland et al. 2010, Filipi et al. 2010), which resulted in similar outcomes to the studies that used 8 weeks.

In all of the studies (n=6) that evaluated isometric strength, torque or power, there was a consistent finding of an improvement in these variables, which was significantly greater than the control group in the DeBolt and McCubbin (2004) study and showed a trend towards being greater in the other 5 studies. The increases ranged from 14.4% to 15.6% (strength), 14.2% to 47.3% (torque) and 23.9% to 47.7% (power). Gait speed also increased in 6 of the studies. Improvements ranged from 0.9% to 18.9%, and were greater than the improvements seen with endurance training (Sabapathy et al. 2011). In three studies, fatigue improved by 9.2% to 26% (Sabapathy et al. 2011, Filipi et al. 2010, Svensson et al. 1994). The three studies that investigated balance also demonstrated improvement following PRT, ranging from 15.4% to 19.9% (Sabapathy et al. 2011, Ayán et al. 2007, DeBolt and McCubbin 2004). On all of these outcomes, as with strength, different measures were used between the studies, limiting the comparability of results.

There was also improvement on some of the other clinical outcomes. Muscular endurance improved in 2 studies and gait distance improved in a further study (de Souza-Teixeira et al. 2009, Ayán et al. 2007, Sabapathy et al. 2011). Quality of life and a functional activity of chair transfer improved in 2 other studies (Sabapathy et al. 2011, Harvey et al. 1999)

2.3.5 NMES Inclusion/Exclusion Criteria

The search of the databases yielded 622 publications. Screening of these publication's title and abstract for the use of an MS population and a NMES intervention was undertaken. Five articles that met these criteria were located. Their reference lists were scanned and no additional articles were retrieved.

The 5 articles were evaluated and met the inclusion criteria of:

- A study population of PwMS.
- A longitudinal design with a NMES intervention was used.
- Outcomes evaluating any of the main problems experienced by PwMS.

2.3.6 NMES Literature

Four of the 5 studies that investigated the use of NMES in PwMS were of low methodological quality, demonstrating a high level of bias (**Table 2**). The most recent study, by Broekmans et al. (2011) had the best methodological quality. An RCT design was employed, however, the non-random group allocation process and failure to blind the assessors resulted in a moderate level of bias. Livesley (1992) also employed an RCT design, but failed to describe the randomization and blinding methods. In addition, this study failed to report the clinical characteristics in terms of disability level of the population, and included three participants with a neurological condition other than MS. Consequently, it scored poorly on the quality scale which limits the generalisability of the results to the MS population.

The generalisability of the other studies (Wahls et al. 2010, Reese et al. 2009, Kent-Braun et al. 1996) is restricted by their small sample sizes. Although the majority of participants in the two retrospective case-based studies (Wahls et al. 2010, Reese et al. 2009) were similar to the population of interest in this thesis due to mobility aid use, the primary outcomes were physiotherapy clinic notes. Consequently, the validity of the results is reduced as some of the outcomes were subjective evaluations by the physiotherapist, rather than a standardized measurement method. Furthermore, reporting of all outcomes in these two studies was incomplete. The quality of the Kent-Braun et al. (1996) study was mainly limited by the non-control group design and lack of blinding. The small number of participants and the heterogeneity of their disability also limit the generalisability of the results.

Table 2 NMES Literature

Study	Population	Study Design	Intervention					Main Findings	Quality Score
			F	I	Type	T	D		
(Broekmans et al. 2011)	n= 33 EDSS 2.5 – 6.5 All MS types	3 arm RCT PRT: n = 11 PRT + NMES: n = 10 C: n = 12	2-3	1x10 – 2x15 50-60% 1 RM, Individually standardized weight progression	Warm-up, Leg press, extension & curl, cool down	60	10 x 2	Quadriceps Torque (Nm) 0-10; 10-20 weeks, % change PRT: 9.9%*† ; 9.3%*† PRT + NMES: 3.2% ; 2.4% C: -2.6% ; -6.9% Hamstrings Torque (Nm) 0-10; 10-20 weeks, % change PRT: 5.2% ; 5.2% PRT + NMES: 6.1% ; 8.1%† C: -6.2% ; -9.4%* Mobility Measures No significant changes – data NR	Met = 3 Unmet = 3 Unclear = 0 Bias = Moderate
			NMES: On/Off: 3 / 4 ; Ramp Up/Down: NR Frequency (Hz): 100; Pulse Width: 400µ Current (mA): Constant - NR Time: 60 minutes; Duration: 10 weeks x 2 Muscles: Quadriceps impaired side						
(Wahls et al. 2010)	n= 9 EDSS 4.5 – 6.5 SP or PP MS only	Retrospective case study series NMES superimposed on progressive exercise Analysed n=7	NMES: On/Off: 12 / 20 ; Ramp Up/Down: 2 / 2 Frequency (Hz): 35; Pulse Width: 300µ Current (mA): Participant controlled (0-100) Time: Daily 15-45 minutes; Duration: Variable Muscles: quadriceps, gluteals & lumbar paraspinals 5 participants used other programmes (FES & spasm reduction) Exercises: Strengthening progressed individually					Days of NMES 33 - 495 Disability (EDSS Change) ; Decreased by 0.5 - 2 points in 7 participants Gait Mechanics (PT observed) 6 participants improved unknown change for 1	Met = 0 Unmet = 6 Unclear = 0 Bias = High

MS: Multiple Sclerosis; **EDSS:** Expanded Disability Status Scale; **Sub:** Subject; **SP:** Secondary Progressive; **PP:** Primary Progressive; **PRT:** Progressive Resistance Training; **Exs:** Exercise; **Secs:** Seconds; **NMES:** Neuromuscular Electrical Stimulation; **C:** Control; **F:** Frequency (days/week); **I:** Intensity; **T:** Time in minutes; **D:** Duration in weeks; **On/Off & Ramp Up/Down:** in seconds; **mA:** milli-amps; **FES:** Functional Electrical Stimulation; **PT:** Physiotherapist; **NARCOMS:** North American Research Committee on Multiple Sclerosis; *****: Significant Difference Within Group; **†:** Significant Difference Compared to Control Group; **- % change:** outcome worse

Study	Population	Study Design	Intervention	Main Findings	Quality Score
(Reese et al. 2009)	N=1 Gait <20 yards, regular scooter use SP MS	Single case study	NMES: programme from Wahls et al 2010. Time: Daily for 20-40 minutes. Duration: 6 weeks, followed by 20 weeks on a dietary intervention. Muscles: paraspinals, abdominals, gluteals, quadriceps, hamstrings, hip flexors and tibialis anterior with voluntary contraction.	NARCOMS QoL 0-6 & 0-26 weeks symptoms & fatigue improved Mobility (PT and Client Observed) 0-6 weeks = Improved endurance 0-26 weeks = Stopped scooter use.	Met = 1 Unmet = 5 Unclear = 0 Bias = High
(Kent-Braun et al. 1996)	N=6 EDSS 2.5-8	Single group pre-post home based intervention with NMES	NMES: On/Off: 2 / 8 (week 1-2) & 2 / 6 (week 3-8) Ramp Up/Down: NR Pulse Width: 300µ Frequency (Hz): 50 Current (mA): Participant controlled Time: 60 minutes Duration: 8 weeks Frequency: 6 days a week Muscle: Tibialis Anterior	Tetanic Force (N) 2.7% increase	Met = 2 Unmet = 3 Unclear = 1 Bias = High
(Livesley 1992)	N=40 (37 with MS, 2 with SCI, 1 with stroke) Disability and MS type NR	RCT NMES & active movement: n=20 C: n=20	NMES with active hip/knee flexion/extension Programme: On/Off: 4 / 4 (secs) Ramp Up/Down: NR Pulse Width: 200µ Frequency (Hz) & Time: 3 for 2 minutes, 10 for 5 minutes and 35 for 5+ minutes. Current (mA): NR Duration: 6 weeks Muscles: Quadriceps and hamstrings C: Sham stimulation.	Spasticity (Subjective) NMES = 5 & 8 participants better (Week 2 & 3 respectively)* C = Non-significant changes Strength (HHD Knee Extension ; Flexion) NMES = 10.3% ; 10.9% C = 27% ; 18.4% Mobility (Rivermead Assessment) No change in either group.	Met = 2 Unmet = 3 Unclear = 1 Bias = High

NR: Not Reported; QoL: Quality of Life; SCI: Spinal Cord Injury; RCT: Randomized Control Trial; C: Control; HHD: Hand-Held Dynamometry; N: Newtons

In all studies except for Kent-Braun et al. (1996), NMES was superimposed upon voluntary muscle contractions of lower limb muscles. The quadriceps was stimulated in four of the studies. Broekmans et al. (2011) was the only study to superimpose the stimulation on a structured PRT programme. The description of the exercise programmes in the remaining studies (Wahls et al. 2010, Reese et al. 2009, Livesley 1992) was unclear. The NMES programme parameters were not consistently reported by all studies. Stimulation parameters in the case report studies were the same, as the Wahls et al. (2010) study was a follow-up on the Reese et al (2009) study. The on/off period, stimulation frequency (Hz), stimulation time, pulse width and duration of NMES use varied between the studies. Both Livesley (1992) and Kent-Braun et al. (1996) used similar lengths of 6 and 8 weeks respectively. Participant controlled current intensity was used in three of the studies (Kent-Braun et al. 1996, Reese et al. 2009, Wahls et al. 2010) and not indicated in the other 2 studies. In determining which NMES parameters produced the best results, the lack of a consistent outcome measure, such as strength, between the studies limits this interpretation.

In the Kent-Braun et al. (1996) study a decrease in strength was shown after the first two days of training, which recovered within a week. The authors attributed this effect to an adaptation to the training. In the other studies, there were no other reports of adverse events or reactions during or following the use of the NMES. Overall, strength and mobility were evaluated in the majority of the studies; however, the outcome measure used differed between the studies. This limits the comparability of the effects of the different programmes.

Strength demonstrated small non-significant increases in the Kent-Braun et al. (1996) and Livesley (1992) studies. In the Broekmans et al. (2011) study, there was a plateau in strength improvements after 10 weeks of intervention in both groups. Significant strength improvements occurred in the PRT group for the quadriceps, and in the NMES group for the hamstrings, compared to the control. The greater improvements in quadriceps strength in the PRT group compared to the NMES group suggest that there was no extra benefit to adding the NMES device to PRT. However, this was not tested statistically. In the case report studies, mobility improved in 6 participants according to the physiotherapist

observation. However, in the Broekmans et al. (2011) and Livesley (1992) studies, which used objective measures of mobility, no improvements were seen in any of the groups. Disability, as rated by the EDSS, improved in all participants in the Wahls et al. (2010) study. The validity of this result is limited though, as the evaluation on the EDSS was performed by a physiotherapist, rather than a trained medical doctor, as the guidelines advise. Fatigue and general symptoms improved substantially on the QoL measure, in the single case study participant. Finally, Livesley (1992) found that spasticity improved significantly in the first weeks with NMES.

2.3.7 Discussion

Summary of the PRT and NMES Literature

The first objective of this review was to identify the main clinical problems that PRT and NMES improved for PwMS who use a walking aid. The results of the PRT literature search firstly revealed that no study has evaluated the effects of PRT exclusively in a cohort of PwMS who use a walking aid, thereby limiting the generalisability of the literature to the population of interest in this thesis. Consequently, identifying the PRT programme parameters that would produce similar results in this sub-group is limited. Nonetheless, improvements in strength, mobility, fatigue and balance occurred following PRT. In four of the studies (Harvey et al. 1999, Ayán et al. 2007, DeBolt and McCubbin 2004, de Souza-Teixeira et al. 2009), there was a concurrent improvement in strength and function related activities, such as balance and mobility. This suggests that strength increases have a positive effect on functional improvement. Only de Souza Teixeira et al. (2009) investigated the relationship between strength and function, demonstrating that mobility and quadriceps muscle power were moderately correlated. Although not clearly defined with statistical testing, the implication is that as a result of the PRT programmes, increases in strength resulted in improved function. This assertion needs to be confirmed in the literature using statistical methods.

In the NMES literature, there is a similar issue relating to lack of generalisability of the results due to the small sample sizes and the heterogeneous nature of the cohorts. In addition, although four of the studies (Livesley 1992, Reese et al. 2009, Wahls et al. 2010) superimposed stimulation on voluntary contraction, the inconsistency and lack of reporting of the NMES and exercise programme parameters restricts conclusions on the most appropriate parameters for improving outcomes. Regardless of these issues, there was no statistically significant improvement in any outcome across the five studies reviewed. There was a trend for strength to improve in three of the studies (Broekmans et al. 2011, Kent-Braun et al. 1996, Livesley 1992); however, it is unclear whether these strength increases were greater than strength training alone, as this was not evaluated. In addition, the generally low methodological quality of the literature precludes any definite conclusion regarding the strengthening benefits of superimposing NMES on voluntary contraction.

Evaluating the quality of the respective intervention literature was the second objective of this part of the literature review. The generally low quality of the research, particularly the NMES studies, is one of the main findings of this review. Biases in the study design that were not appropriately addressed are the primary reason for the low quality of the research. Specifically, there is a lack of studies using a randomized control design and adequate blinding practices of the investigators. As a result, a clear understanding of the effects of PRT and NMES interventions in PwMS is restricted. This limits the determination of a best evidenced based protocol that combines PRT and NMES for PwMS who use a walking aid, which is the primary objective of this section of the literature review.

Protocol Combining PRT & NMES

In designing a PRT programme for PwMS, completing the exercises 2-3 times a week resulted in significant strength and functional improvements in the majority of the studies in the present literature review. This is in line with the American College of Sports Medicine (ACSM) guidelines for strength training in novices (Ratamess et al. 2009). In the NMES literature, the only study that combined NMES and PRT (Broekmans et al. 2011) also used an intervention

frequency of 2-3 times a week, and no adverse reactions were reported. Considering the initial muscle weakness associated with PRT and NMES (Cheung et al. 2003, Kent-Braun et al. 1996), the training frequency of 6-7 times a week used by 3 of the NMES studies (Wahls et al. 2010, Reese et al. 2009, Kent-Braun et al. 1996), was judged to be inappropriate due to increasing the risk of falls in this balance-impaired population. Therefore, starting with a training frequency of twice a week and increasing it to three times a week was deemed suitable, to allow participants to become accustomed to the exercise.

The majority of the PRT studies used a programme of 6-8 weeks in duration, resulting in significant or large improvements in strength, power or torque. Considering the length of the programmes, the resistance training physiology literature (Gabriel et al. 2006) indicates that these improvements are likely to be primarily due to neural adaptations rather than hypertrophy. Since muscle size is recognised as playing a primary role in strength (Huygens et al. 2004), programmes of longer duration than 8 weeks would appear to be necessary, in order to achieve substantial strength increases, particularly in a population with muscle weakness and atrophy. Previously, PRT programmes of 12 to 20 weeks with and without NMES have been shown to be well tolerated in PwMS with mild to moderate disability, and result in significant strength increases (Dalgas et al. 2009, Broekmans et al. 2011). Furthermore, Dalgas et al (2010b) showed that a 12 week PRT programme is sufficient to achieve a significant increase in muscle CSA in PwMS. In the health population, programmes of 12 weeks or greater have also been shown to be effective in significantly increasing muscle CSA (McCall et al. 1996, Welle et al. 1996, Häkkinen et al. 2000). Therefore, a programme of 12 weeks was considered appropriate to improve outcomes for the present study.

In the PRT literature, the majority of studies used a training intensity of 2-3 sets of 8-12 repetitions to fatigue, which is the recommendation of the ACSM guidelines (Ratamess et al. 2009). In order to maintain the intensity of training as participant's strength increases, weight can be added to the limb when the exercise is completed without fatigue. This method was used by Harvey et al. (1999) and Broekmans et al. (2011), and resulted in significant torque increases.

In addition, adapting the intensity of the exercise to the individual is clinically relevant considering the variability associated with MS. Furthermore, from an adherence point of view in the home setting, it has been shown that if the exercise intensity is high, participants are likely to complete less exercise (Perri et al. 2002). Therefore, for the present study a training intensity that is individualised to the participant's ability in terms of sets, repetitions and weight using a maximum of 3 sets of 12 repetitions to fatigue was deemed suitable.

In the PRT literature, the length of intervention session that results in significant improvements is unclear, as it was not reported consistently. Similarly, determining the optimal length of intervention session in the NMES literature is limited by the inconsistent effects seen. The results of the systematic review by Glinsky et al. (2007) suggest longer stimulation times result in higher strength gains. However, the majority of these studies used stimulation without active contraction, which allowed for prolonged treatment times. This is not feasible in the present study. Since the NMES device (Kneehab - ® manufactured by Biomedical Research, Ltd) is designed for the quadriceps, the number of quadriceps exercises, the training intensity (sets and repetitions) that the individual completes and the on period of stimulation will determine the length of stimulation. Programme 1 on the device (**Table 3**) was deemed most appropriate as it uses a high frequency (Hz), which has been shown to increase force output in PwMS and healthy adults (Ng et al 2004), and has a shorter relaxation time than programme 3. Four quadriceps exercises was considered suitable for the present PRT programme, as 3-5 exercises were used and well tolerated in previous PRT studies (Taylor et al. 2006, DeBolt and McCubbin 2004, Sabapathy et al. 2011, Dalgas et al. 2009). Given that global weakness of the lower limbs is a feature of MS (Schwid et al. 1999), 2 additional lower limb exercises were judged to be suitable for inclusion. Consequently, if participants completed 3 sets of 12 repetitions of each quadriceps exercise with the 5 seconds of stimulation, they would receive 12 minutes of stimulation per session, which is greater than the stimulation time in the Broekmans et al. (2011) study.

Table 3 Kneehab Device Programmes

Program	Frequency (Hz)	On (seconds)	Off (seconds)	Ramp-up (seconds)	Ramp-down (seconds)
1	50	5	10	1	0.5
2	35	5	5	1	0.5
3	50	10	50	1	0.5

In the MS case studies (Wahls et al. 2010, Reese et al. 2009) the intensity of the NMES current was controlled by the participant. This may have been an important factor in participants' prolonged use of NMES device. Setting the intensity of the current at a high level may lead to discomfort and non-compliance. Therefore, by allowing the participant to set the intensity of the current at their maximal tolerable level, high compliance is more likely and another component of the programme can be progressed. This approach was used in the present study.

Chung et al (2008) found that knee extensor strength was asymmetrical in PwMS, which supports the clinical observation of unilateral impairment. Asymmetry in leg strength was also shown to be significantly associated with gait speed and balance (Chung et al 2008). This suggests that targeting strengthening unilaterally may benefit functional impairments. As a result, for the present study, a PRT programme of unilateral training, primarily, was deemed appropriate. In terms of safety, it was also realised that bilateral training with two Kneehab devices simultaneously may be difficult to co-ordinate for participants. Although bilateral training could have been achieved by completing unilateral exercises on both sides, it was recognised that this would have increased the exercise demands substantially in terms of time and number of exercises to be completed. In an already highly fatigued population, this was considered inappropriate as it may impact on ability to perform other ADL and may have lead to non-compliance.

A final consideration for implementing a combined PRT and NMES protocol in the home setting is the issue of supervision. Although both interventions have been recognised to be safe and tolerable individually, they have not been investigated as a combination in the home setting with a more disabled group of

PwMS. Therefore, piloting is important. In addition, Dalgas et al. (2008) highlighted the importance of supervision in terms of adherence to the programme. In order to achieve this in the home setting, previous studies have used regular telephone calls (Harvey et al. 1999, DeBolt and McCubbin 2004). In the DeBolt and McCubbin (2004) study there was 95% compliance with the programme, indicating that telephone contact was an effective method to ensure compliance. Therefore, this would appear to be an appropriate approach for the present study also.

2.3.8 Conclusion

In conclusion, the literature supporting PRT in PwMS is of moderate to low quality and the NMES literature in MS is of very low quality. Therefore, developing a best evidence based protocol to combine PRT and NMES requires the clinical considerations of the population, the nature of the interventions and in particular the setting, as this influences the intervention protocol and the supervision method. With these considerations and the present literature in mind, a combined PRT and NMES programme of 12 weeks duration, with a training frequency of twice a week for the first 6 weeks and 3 times a week for the second 6 weeks, an individualised intensity of a maximum of 3 sets of 12 repetitions to fatigue using 6 lower limb exercises (4 of the quadriceps), was deemed to be appropriate for the present study. Participant controlled current intensity and weekly phone contact were also considered important in order to ensure compliance with the programme.

2.4 Conclusion

In this two part review of the MS literature, the clinical profile of PwMS and the effects of PRT and NMES in PwMS were investigated. Overall, the main finding was that PwMS experience a number of problems, which can be improved by PRT, particularly muscle strength and physical function. The manner in which improvements in physical function occurred due to the PRT is not well understood. This is primarily due to a lack of studies investigating the relationships between strength and functional outcomes in PwMS. Similarly, the

benefits of adding NMES to PRT in PwMS are unclear, due to the low number and quality of the studies. Theoretically, superimposing NMES on voluntary contraction will result in increased muscle activation (Adams et al. 1993) and greater neuroplastic changes (Kimberley et al. 2004). As a result we would expect functional improvements. Therefore, in order to establish the effects of adding NMES to a PRT programme in PwMS, there is a need for a well-designed randomized controlled study to compare PRT to the same programme with an NMES device.

CHAPTER 3 – METHODS

3.1 Introduction

In this chapter the methods employed to evaluate the effects of adding a NMES device to a home based PRT programme for PwMS who use a walking aid are outlined. The literature review (**Chapter 2**) highlighted that study design flaws were the main weaknesses in the PRT and NMES literature. Therefore, a rigorous study design was used in the present study and is described in detail to allow others to evaluate the study. Furthermore, the literature review emphasised the importance of the setting to intervention implementation. In selecting outcome measures for the study, the suitability of the measure to the home setting is also an essential consideration. Thus, both the intervention implementation and outcome measurement selection are outlined with the home setting in mind.

3.2 Aims and Objectives

The aim of this chapter is to outline the methods used in the present study. The objectives were:

1. To describe the study design.
2. To describe the implementation of the proposed intervention.
3. To outline the outcome measures and related protocols used.

3.3 Ethics Committee Approval

Approval for this study was granted by the University of Limerick Education and Health Sciences Ethics Committee. Written informed consent was obtained from participants during the pre-intervention visit, prior to data collection (see **Appendix 2**).

3.4 Participants

3.4.1 Recruitment

Men and women with MS were recruited in the West and Mid-West regions of Ireland through the respective regional offices of the MS Society of Ireland (MSSI). Administrators in these offices identified all members on their list that were known to use a walking aid to mobilise, as this was one of the primary eligibility criteria. Each regional list was subsequently randomised, and the first 40 members were sent the subject information leaflet (**Appendix 3**), and a letter notifying them of the study. In addition, notification that participants were being sought was placed on the MSSI website with the subject information leaflet. The recruitment period lasted 2 months (April to May 2010).

The blinded assessor was contacted by men and women volunteering their participation. During the initial telephone call the blinded assessor ensured that volunteers had read the subject information leaflet, and had any questions relating to the study answered. The blinded assessor explained the trial procedure to ensure the volunteer had a clear understanding of what their participation would involve. At this point, if volunteers were still interested in participating they were screened for their eligibility.

3.4.2 Eligibility criteria

Inclusion Criteria

The criteria for inclusion were:

1. An age of 18 years or older.
2. A diagnosis of Multiple Sclerosis by a consultant neurologist (confirmed by the participant).
3. A score of 2, 3 or 4 (unilateral support, bilateral support or wheelchair outdoors to mobilise) on the lower limb disability component of the Guys Neurological Disability Scale (GNDS) (Sharrack and Hughes 1999).

Exclusion Criteria

Volunteers were excluded if they:

1. Met any of the contra-indications to electrical stimulation which were:
 - a. a lack of normal sensation (confirmed with sharp/blunt and light touch tests)
 - b. pregnancy
 - c. presence of a pacemaker
 - d. presence of metal implants (in lower limbs)
 - e. comprehension difficulties due to cognitive issues (screened by asking participants to repeat the outline of the protocol back to the blinded assessor during initial telephone call)
 - f. a history of cancer or epilepsy.
2. Were participating in a supervised exercise programme (aerobic, resistance or mixed) currently or in the past month. This criterion was chosen to ensure participants' baseline measures were reflective of their actual status, without the influence of other exercise.
3. Had experienced a relapse in their MS in the past three months as complete recovery on the EDSS has been shown to be significantly higher at 3 and 6 months (Iuliano et al. 2007).
4. Had an acute injury to the lower limb that would be exacerbated by lower limb resistance exercise.

There was no restriction on type of MS for the purposes of analysis in the main study, as it was considered important to gain a preliminary understanding of the effects of the interventions on MS subtypes.

3.5 Study Design

A single blind two arm block-randomized experimental design was employed. All participants were tested in their homes on three occasions; pre-, mid- and post-intervention (week 0, 6 and 12) by the blinded assessor (a chartered physiotherapist). A follow-up investigation was not feasible due to time-constraints. Following pre-intervention testing, participants were taught the lower limb PRT programme by the blinded assessor.

The randomiser assigned participants to group A (PRT), or group B (Kneehab), as they entered the study, using a pre-determined block randomized order. This order was devised by the randomiser, to conceal randomization and blind the assessor to group allocation. The randomisation sequence was generated by placing a block size of 6 (3 treatment and 3 controls) into an envelope and drawing and replacing until a stream of 60 randomisations was generated. A block size of six was deemed appropriate as smaller block sizes are recommended for clinical trials with a small sample, in order to control the balance of group numbers (Kang et al. 2008).

The randomiser informed the NMES deliverer (a physiotherapist) of participants assigned to the Kneehab group and which was their more impaired side (this was based on subjective report). Within one week of pre-testing the Kneehab device was delivered to Kneehab group participants for their impaired side by the NMES deliverer. Participants were taught how to use the device with the PRT program. The intervention was targeted at participants' weaker side as unilateral impairment is a common clinical presentation in PwMS.

3.6 Intervention Procedure

The development of the PRT and Kneehab protocols was based on the findings of the literature review (**Chapter 2**), in the context of suitability to the home setting.

3.6.1 Neuromuscular Electrical Stimulation Programme

The Kneehab ® device is a CE marked neuromuscular electrical stimulation device. The device is a synthetic garment that is applied to the anterior thigh and held in place using Velcro straps (**Figure 1**). The device consists of 4 electrodes strategically placed to activate the quadriceps muscle through a novel Multipath ® system. The Multipath ® system works by creating any combination of current pathways between electrodes. This is proposed to enhance the spatial distribution of the stimulation current, thereby improving comfort (Feil et al. 2011). This is demonstrated in **Figure 2** (Feil et al. 2011).



Figure 1 KneeHab Device

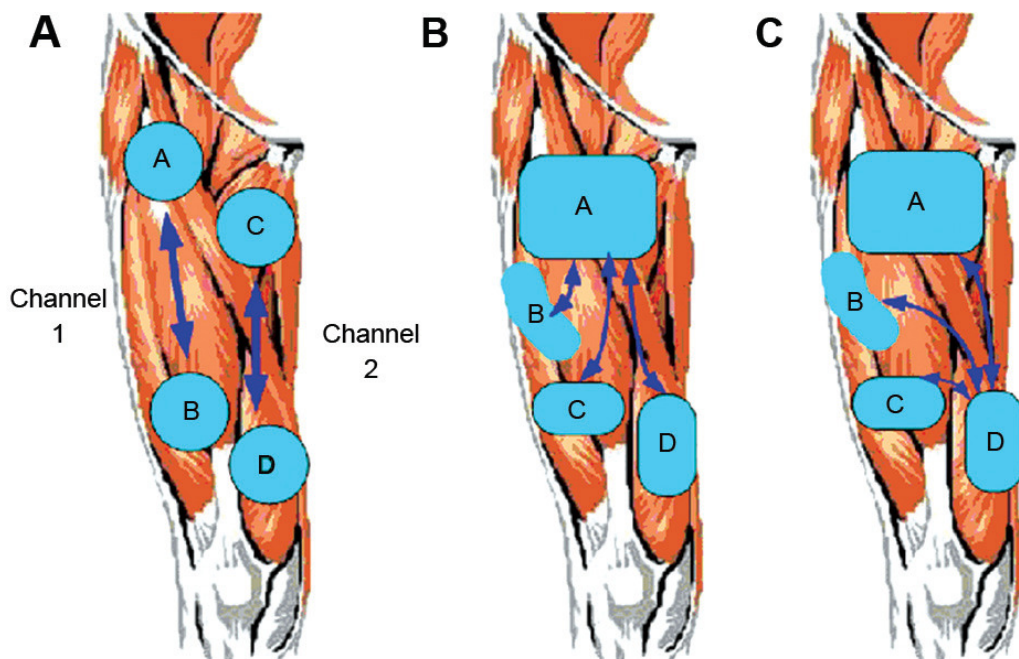


Figure 2 Distribution of Stimulation Current in Traditional (A) and KneeHab (B + C) Devices

Device Parameters & Programs

The KneeHab ® device uses a symmetrical biphasic square waveform. The width of the pulse varied during stimulation from 100-400 μ s. The voltage of the device also varies between 500 Ω – 1.5 K Ω during stimulation impulses. The device contains two channels with a 1 second delay between channels 1 and 2. This results in channel 1 starting its ramp-up 1 second before channel 2, which ensures recruitment of the Vastus Medialis Oblique prior to the rest of the quadriceps muscle. The range of current available on the device is between 0 and 99 milliamps (mA). There are three set programs available on the device

(**Table 3**). Programme 1 was used, which uses a frequency of 50Hz, on/off time of 5/10 seconds, ramp up/down of 1/0.5 seconds.

3.6.2 Progressive Resistance Training Programme

PRT Protocol

Based on the literature review (**Chapter 2**), a 12 week PRT programme with an exercise frequency of twice a week from weeks 1 to 6 and three times a week from weeks 7 to 12 was employed. Similar to the PRT studies in the literature review, participants were advised to avoid performing the exercises on consecutive days to allow for muscular recovery. A programme of 6 exercises was deemed appropriate by the literature review, with 4 quadriceps exercises in order to maximise use of the Kneehab. For each exercise, participants were encouraged to progress from 1 set of a maximum of 12 repetitions to a maximum of 3 sets of 12 repetitions, by exercising to fatigue [failing to complete last repetition with full range of movement - (Taylor et al. 2006)]. Once 3 sets of 12 repetitions could be completed without fatigue, weight was added to the exercise, in increments of 0.5 or 1 kilogram and the number of sets and repetitions was gradually increased to the maximum. Participants were advised on progression during a weekly phone call with the blinded assessor. Rest periods of 2 to 3 minutes between sets and exercises were advised.

Exercises

The PRT programme consisted of 6 lower limb exercises which are outlined in **Table 4**. In determining the content of the PRT programme, the main considerations for exercise inclusion were:

- Suitability for the home setting i.e. safe and minimal equipment costs
- Type of exercises, in terms of strengthening potential and functional relevance

The use of free weight exercises only was necessary as the intervention was taking place in the home setting. In selecting the type of exercises to be included in the programme, the strengthening potential and functional relevance of the exercises were considered important. Previous PRT studies in the MS

population have demonstrated positive strength and functional outcomes, when using a combination of open and closed kinetic chain exercises, with concentric and eccentric phases (Dalgas et al. 2009, DeBolt and McCubbin 2004). In the present study, a PRT programme with a mix of exercise types was employed. Open kinetic chain (OKC) exercises of the quadriceps have been demonstrated to increase training load and produce higher electromyographic output than closed kinetic chain (CKC) exercises in healthy adult populations (Augustsson et al. 1998, Andersen et al. 2006). Thus, indicating the potential for higher strength gains. In addition, significant improvements in functional strength have been demonstrated following CKC exercises (Augustsson et al. 1998). The improvement in functional performance following CKC exercise is attributed to the specificity of the training (Stone et al. 2007). The incorporation of concentric and eccentric phases of contraction in the exercises is justified on the basis that the strength of both are decreased in PwMS, compared to controls (Ponichtera et al. 1992), and can be increased with respective training of each (Higbie et al. 1996).

A list of suitable exercises was developed which included sit-to-stand, lunges, static quads, hip extension in standing and the exercises in **Table 4**. Initially, the blinded assessor trialled the quadriceps exercises with the Kneehab device. The sit-to-stand and lunge exercises were deemed unsafe, due to the need to time the extension phase of the movement with the stimulation of the device, which was expected to be problematic for PwMS considering the difficulties they experience with sit-to-stand and balance. Subsequently, a pilot of the remaining exercises using the Kneehab devices was undertaken with a volunteer who met all eligibility criteria. No adverse events occurred while the volunteer was trialling the exercises. Hip extension in standing was excluded due to the tendency to use compensatory trunk flexion. Finally, the static quads exercise was ruled out as it was recognised that progression with weight would not be possible.

Table 4 PRT Programme Content, Order & Weight

<i>Exercise</i>	<i>Description (One Repetition)</i>	<i>Weight</i>
1. Squats*	Standing with supportive surface in front. Knees flexed slowly as far as possible, without heels rising. Hold for 5 seconds. Knees extend slowly to the count of 5 seconds. Rest for 5 seconds and repeat.	In bag over shoulders
2. Calf-Raises	Standing with supportive surface in front. Push-up on toes slowly. Hold for 3 seconds. Lower slowly. Rest for 5 seconds and repeat.	In bag over shoulders
3. Step-Ups*	Place weaker foot on step or wooden box with supportive surface in front or at side. Slowly extend knee to the count of 5 seconds. Flex knee slowly. Rest for 5 seconds and repeat.	In bag over shoulders
4. Side-Stepping	Standing with supportive surface in front. Step to one side and bring feet together. Step back and bring feet together. Repeat.	In bag over shoulders
5. Knee Extensions*	Sitting with knees at 90°. Slowly extend the weaker knee to the count of 5 seconds. Allow knee to flex slowly to start position. Rest for 5 seconds and repeat.	Ankle (around malleoli)
6. Inner Range Quads*	Lying with a bottled wrapped in a towel under the back of the weak knee. Extend knee slowly to the count of 5 seconds. Flex knee slowly to start position. Rest for 5 seconds and repeat.	Ankle (around malleoli)

* Quadriceps Exercises; Pictures of all exercises are in **Appendix 4**.

Since the aim of the intervention was to strengthen the more impaired side, participants were advised to perform the step-up, knee extension and inner-range quad exercises with the more impaired side only. The other 3 exercises were performed bilaterally. The order of the exercises was based on the PRT guidelines provided by the ACSM (Kraemer et al. 2002), which were endorsed in a review of PRT for PwMS (Dalgas et al. 2008). Exercises using large muscle

groups and multiple joint exercises were performed first, followed by exercises using small muscle groups and single joint exercises.

The use of 5 second contractions and 10 resting periods between repetitions were used to mimic the length of the contract/relax periods of stimulation provided by the Kneehab device.

3.6.3 Intervention Fidelity

Intervention fidelity refers to the completion of the intervention as planned (Horner et al. 2006). Since the intervention in the present study was not supervised, employing intervention fidelity strategies were recognised as important, to enhance the internal validity of the study.

In order to achieve effective intervention fidelity, there are a number of goals to consider (Bellg et al. 2004). These goals include; standardizing skills and training of interventionists, ensuring participants comprehension and ability to participate in the intervention, monitoring the intervention that each group receives and ensuring adherence to the intervention. A number of strategies were employed to meet these goals.

First, the teaching methods and skills of the investigators delivering the intervention were standardized using a practice teaching session. Participants' comprehension and ability to perform the exercises were ensured by providing a thorough teaching session, exercise manual and checking ability to perform the exercises. In order to verify the extent to which the intervention was completed as intended, participants received exercise diaries. In addition, during the blinded assessors' weekly phone calls to participants the volume of exercise completed in the most recent session was recorded. The weekly phone calls were also used to encourage continued adherence to the intervention by answering any questions, motivating participants to continue and advising on exercise progression. In addition, participants in the Kneehab group received a phone call from the NMES deliverer every second week, to deal with any difficulties they may be having with the device.

3.6.4 Teaching PRT

Prior to commencing recruitment, the blinded assessor and the NMES deliverer met to ensure the PRT with and without the Kneehab device would be taught in a standardised manner. This was aimed at preventing confusion for participants receiving the device as they would be taught the programme on two occasions. In addition, both investigators had the opportunity to practice the teaching of the programme and identify any difficulties or changes that were necessary. A person with MS volunteered to participate in the pilot teaching. An exercise booklet (**Appendix 4**) designed for the PRT programme was used during this practice, during initial teaching of the programme and given to participants. A modified version of the booklet was also designed for Kneehab participants with instructions how to apply the device (**Appendix 5**). Following the pilot teaching, the investigators identified the need to ensure participants understood how to perform the exercises. Therefore, it was decided that following initial teaching participants would be asked to demonstrate 3-4 reps of each exercise.

Teaching participants the respective programmes involved the following steps:

1. At the start and end of the session, the potential for muscle soreness and risk of increased symptoms during exercise was strongly highlighted. Appropriate advice was provided on how to deal with both scenarios.
2. Demonstration of the exercise technique by the investigator while using the booklet to show the written and pictorial steps.
3. Performance of each exercise to fatigue by the participant following the PRT protocol. The investigator provided feedback on participant's technique and wrote specific cues in the booklet that encouraged the correct technique with the exercise.
4. Participants demonstrated 3-4 reps of each exercise, and any further feedback necessary was provided.

3.6.5 Exercise Diaries

Participants were provided with exercise diaries to record the number of sets and repetitions they performed for each exercise, how long they exercised for and for those who received the Kneehab device, at what current intensity the device

was set for each exercise. The investigator demonstrated on the first day how to record the exercise completed. Exercise diaries were collected at the end of the intervention for analysis of volume of exercise completed.

3.6.6 Blinding

There was a risk of the blinded assessor becoming aware of participants' group allocation due to the weekly phone calls and two follow-up visits. To reduce this risk the blinded assessor reminded participants at the start of every phone call and follow-up visits to avoid indicating their group allocation. A record was maintained of any incidences where group allocation was revealed.

3.7 Outcome Measures

Prior to baseline outcome measurement the blinded assessor interviewed participants regarding the history of their MS, main symptoms and problems, their physical activity levels in the past four months and medical/non-medical treatment in the past year.

Participants were evaluated at a similar time of day (within 1 hour of the baseline measurement time of day) on the mid- and post-intervention follow-ups. This was considered important as diurnal variations in symptoms in PwMS (Morris et al. 2002) may affect the reliability of physical measurements. Some of these outcome measures required physical activity and the measurement of internal factors.

In determining whether a measure was appropriate for the outcome to be evaluated, the robustness of the measure's psychometric properties and the logistical suitability of the measure in the home setting were considered.

3.7.1 Impairment Outcome Measures

Muscle Strength Measurement

The measurement of quadriceps muscle strength was the primary outcome measure of interest. The strength of the plantar-flexors and gluteus maximus were also measured.

Isokinetic dynamometry (IKD) is recognised as the gold standard in strength measurement (Martin et al. 2006, Drouin et al. 2004). However, due to the logistics of the present study, IKD was unsuitable as it is both expensive and non-portable. Hand-held dynamometers (HHD) were considered an acceptable alternative due to their portability and low cost. The validity and reliability of HHD has not been investigated in PwMS however, in other neurological populations these psychometric properties have been established (Kolber and Cleland 2005). The measurement protocols varied in these reliability studies. Therefore, in the following section these studies will be compared to determine the most reliable protocol. For the purpose of the present study the intra-rater reliability only was of interest, as all measurements were carried out by the blinded assessor.

Brief Review of the HHD Reliability Literature

In **Table 5** the studies investigating the intra-rater reliability of knee extension strength measurements are outlined. All studies used the same testing position of the participant and application of the HHD. Superior reliability was demonstrated when the mean of 3 measures was calculated instead of a single measure (Riddle et al. 1989, Taylor et al. 2004, Busse et al. 2008).

Table 5. Reliability of Knee Extension Strength Measurement

Study	Participant Position	HHD Position	Type of Test	Results
(Bohannon 1986)	Sitting, hip & knee at 90°	Proximal anterior ankle	Make	r= 0.97 – 0.98
(Riddle et al. 1989)	As above	As above	Make	1 Measure: ICC= 0.79 Mean 3 Measures: ICC= 0.82
(Taylor et al. 2004)	As above	As above	Make	ICC= 0.81
(Busse et al. 2008)	As above	As above	Not reported	1 Measure: ICC= 0.87 Mean 3 Measures: ICC= 0.95

r = Pearsons Product-Moment Correlation; **ICC** = Intra-class correlation

All plantar-flexion strength measurement studies demonstrated high reliability, but differed in participant positioning (**Table 6**). A supine position was deemed more suitable, as stabilisation of the limb is important to achieve greater reproducibility of measurements (Kolber and Cleland 2005). Therefore, Bohannon’s (1986) method appears most suitable, as placing the knee in extension requires less stabilisation by the participant, which is important considering the muscle weakness experienced by PwMS.

Table 6. Reliability of Plantar-Flexion Strength Measurement

Study	Participant Position	HHD Position	Type of Test	Results
(Bohannon 1986)	Supine, hip & knee extended	Metatarsals on plantar surface	Make	r= 0.97 – 0.98
(Taylor et al 2004)	Supine, knee flexed 90°	As above	Make	ICC= 0.96
(Busse et al 2008)	Sitting, hip & knee at 90°	As above	Not reported	1 Measure: ICC= 0.95 Mean 3 Measures: ICC= 0.98

r = Pearsons Product-Moment Correlation; **ICC** = Intra-class correlation

For hip extension strength testing, all studies used the same application point for the HHD but differed in participant positioning (**Table 7**). The highest reliability was shown when participants were tested in standing supported by a plinth; however, the type of test used is not described (Busse et al. 2008).

Although, the method used by Bohannon (1986) demonstrated higher reliability than Taylor et al. (2004), the position was anticipated to be difficult to maintain during the test due to the muscle weakness experienced by PwMS.

Table 7. Reliability of Hip Extension Strength Measurement

Study	Participant Position	HHD Position	Type of Test	Results
(Bohannon 1986)	Supine, hip & knee at 90°	Posterior thigh	Make	r= 0.87 – 0.95
(Taylor et al. 2004)	Prone, knee & thigh extended	As above	Make	ICC = 0.88
(Busse et al. 2008)	Standing facing a plinth, legs extended	As above	Not reported	1 Measure: ICC= 0.97 Mean 3 Measures: ICC = 0.99

r = Pearsons Product-Moment Correlation; ICC = Intra-class correlation

Kolber and Cleland (2005) have indicated that sufficient stabilisation of the limb is important for a reliable protocol. In the Bohannon (1986) and the Taylor et al. (2004) studies this was demonstrated as the limb was stabilised proximally for the three muscles tests, all of which demonstrated moderate to high reliability. In all of these studies a 5 second contraction was used. Participants built up to their maximal contraction for the first 2 seconds and for the final 3 seconds produced their maximal contraction. The preferable type of test to be used was unclear as none of the studies used a “break” test (tester exceeds the force of the participant). A comprehensive review of the literature has indicated that “make” tests (tester matches the force of the participant) produce greater reliability in healthy and impaired populations (Kolber and Cleland 2005). Therefore, a 5 second “make” test with proximal stabilisation of the limb was deemed suitable.

Measurement Protocol:

A JTech Power Track II ® (JTech Medical) HHD was used for all testing (**Figure 3**). The range of measurement was 0-220 Newtons (N). For the testing of the three muscles:

- Standard verbal instruction and a demonstration of the movement required were given to participants prior to testing. A trial test was

performed to ensure correct technique by the participant and sufficient stabilisation by the tester.

- The muscle group of each leg was tested 3 times. Tests were alternated between legs to provide a rest for the exercised limb.



Figure 3. Hand-Held Dynamometer

Quadriceps strength was measured as demonstrated in **Figure 4** with the HHD applied to the ankle anteriorly and the thigh stabilised by the assessor.



Figure 4. Quadriceps Strength Measurement Procedure

Plantar-flexion strength was measured as demonstrated in **Figure 5**, with the ankle in 90°, the HHD applied to the plantar aspect of the metatarsal heads and the lower leg was stabilised anteriorly by the assessor.



Figure 5. Plantar-Flexor Strength Measurement Procedure

Gluteus Maximus strength was measured as illustrated in **Figure 6**, with the HHD applied to the posterior thigh immediately above the knee and the opposite hip was stabilised by the assessor.



Figure 6. Hip Extension Strength Measurement Procedure

Quadriceps Endurance

Repeated Sit-To-Stand Test

In determining an appropriate test, the influence of the specificity principle of exercise training was considered. This principle indicates that by training a muscle using a certain exercise, i.e. knee extension, the outcomes of strength or endurance when tested under a similar condition, i.e. knee extension, will be greater than if a different condition was employed, i.e. leg press. Consequently, repeated knee extension in sitting was excluded as an option for evaluating endurance, as it was one of the exercises in the PRT programme. Instead a

repeated sit-to-stand (STS) test was decided upon. Although, this action is similar to the squats exercise, it was deemed suitable as the range of movement and availability of support would not be the same. In addition, a functional test was considered more clinically relevant.

Previous studies using a repeated STS test to measure muscular endurance have employed a time limit within which the maximum number of repetitions possible were to be completed (Netz et al. 2004, Bohannon 1998). Considering that local muscular endurance is defined as the maximal number of repetitions performed with a specific training load (Ratamess et al. 2009), a time limitation to completion of maximum repetitions was deemed inappropriate.

Testing Protocol

Participants sat in a chair with a back support, no arm rests and a seat height of 45cm. Although chair seat height is recognised as a determinant of STS performance (Janssen et al. 2002), an adjustable height chair could not be obtained. For the test, participants were instructed to stand up and sit down as many times as they could until they were unable to do anymore due to fatigue. The use of arm rests has also been found to be a determinant of STS performance (Janssen et al. 2002). As a result participants were instructed not to use their hands for support at any stage or they would be stopped. In addition, participants were stopped if they sat for more than 3 seconds or failed in an attempted STS. Both of these scenarios were considered signs of fatigue.

Quadriceps Thickness Measurements

Real-time Ultrasound

Magnetic resonance imaging (MRI) and computed tomography (CT) are widely acknowledged as the gold standard in muscle size measurements (Perkin et al. 2003, Pretorius and Keating 2008). However, both of these methods are very expensive, lack portability and CT exposes participants to ionising radiation. Real-time ultrasound (RTUS) is a low cost, safe and portable alternative.

The validity of RTUS has been confirmed for the measurement of muscle CSA and thickness, across a variety of populations and muscle groups, including

quadriceps (Pretorius and Keating 2008). To date, a reliable method of measuring quadriceps muscle size is unclear due to issues with the inconsistent alignment of the transducer perpendicular to the muscle, inconsistent pressure applied through the transducer (Dupont et al. 2001), and reporting the method of scanning point location in sufficient detail for reproducibility.

Two studies evaluated the reliability of measuring the CSA of the rectus femoris (RF) and vastus intermedius (VI) quadriceps muscles (Bemben 2002, Howe and Oldham 1996). These studies reported moderate to high intra-class correlation (ICC) values (0.72-0.88, 0.98-0.99) and mean differences of 0.01-0.26cm, 0.6-1.1cm, respectively. In the Bemben (2002) study, the variability associated with the protocol is unclear as the context of the mean size of the muscle is not provided. Low variability is indicated in the Howe and Oldham (1996) study, as the majority of points on the Bland and Altman plots are close to zero. However, in both studies the transducer was applied perpendicular to the thigh rather than the muscle and the method of minimising pressure was not explained. Pretorius and Keating's (2008) assertion that accurate pictures should have clearly definable muscle borders, indicates that the visibility of the muscle borders can be used to overcome these issues. Additionally, the location of the scanning point in the transverse plane was not described in either study. The point should be located along a line between an inferior and superior reference point, as has been done in other non-reliability studies (O'Sullivan et al. 2009, Seymour et al. 2009). In order to address these issues, a novel measurement protocol was developed.

Measurement Protocol:

The Logiq-e (General Electrics ®) RTUS machine was used. The frequency of the RTUS machine was set at 8 MHz, using a virtual convex setting and the focus positions were adjust to improve the illumination on the screen. A linear transducer was used. The protocol involved:

- Taking 3 measurements of the CSA of the quadriceps (RF and VI) on each leg.

- The participant lay supine with their knee extended and their heel in a custom made device to maintain the hip in neutral rotation (**Figure 7**). This was used as PwMS may be unable to maintain this position independently due to muscle weakness or spasticity.

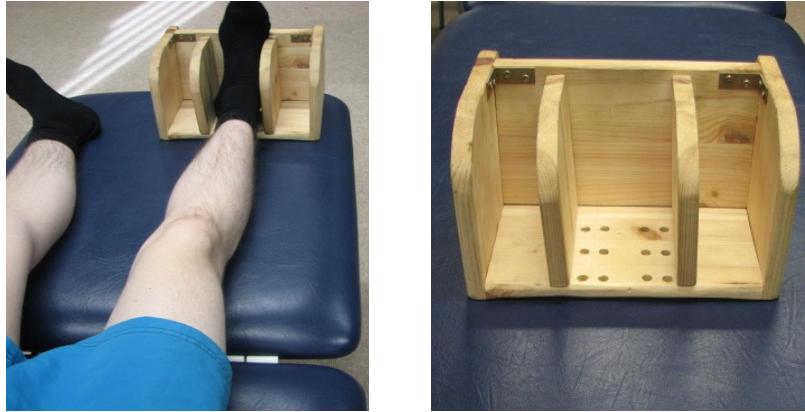


Figure 7 Leg Positioning Device

- The scanning point was located by marking the mid-point of the thigh (mid-point of patella superiorly to the most inferior point of the anterior superior iliac spine) (**Figure 8**). All measurements were recorded and used in follow-up evaluations, to enhance scanning point relocation.
- Vertical and horizontal lines (a cross) were drawn using the edge of the tape measure. This cross provided an alignment guide when scanning.
- A 10 millimetre (mm) wide steri-strip was placed on the vertical line (**Figure 8**), to provide a shadow on the image when scanning. This is proposed to improve reproducibility (Dupont et al. 2001), and provides a reference point on the image for consecutive measurement.

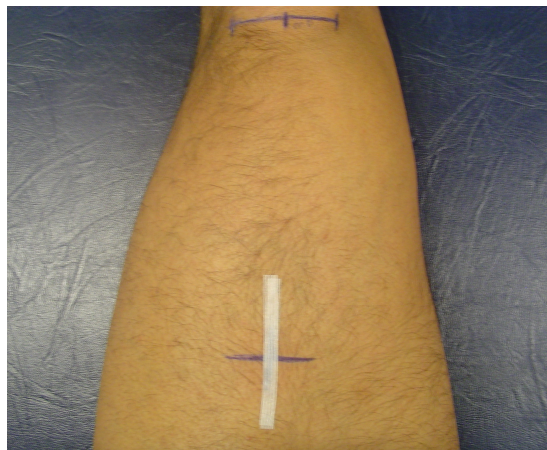


Figure 8 Marking of the Thigh

- Ultrasound gel was placed over the horizontal line and the transducer was applied perpendicular to the thigh.
- The position of the transducer was changed in the transverse and sagittal plane until the clearest image of the muscle borders was found. It was ensured that the shadow provided by the steri-strip appeared in the middle of the muscle belly, perpendicular to the muscle borders.
- The pressure applied through the transducer was reduced and increased until the clearest image with the least amount of pressure was found.
- The image was frozen and a line was drawn between the superficial and deep borders of the muscles at the closest point to the shadow (Figure 9). These lines identified the measurement points of interest.

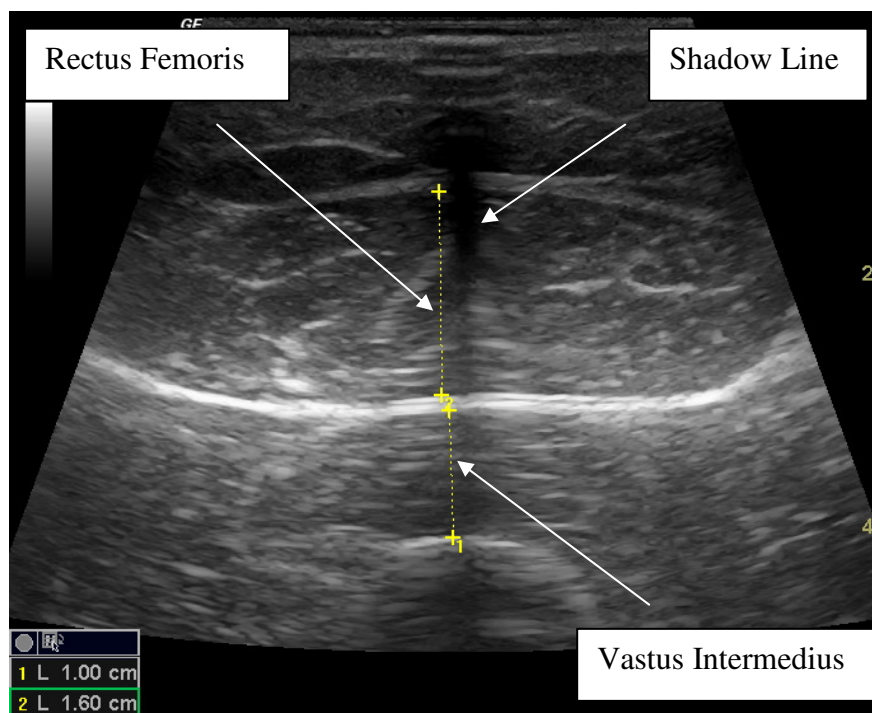


Figure 9 Example of Ultrasound Image

Measurement of Thickness using Software

The thickness of the muscles was measured using the Image J Processing and Analysis ® software programme. After setting the scale, two vertical lines were drawn and measured, which were parallel to the shadowed line provided by the steri-strip. The drawn line was as close to the shadowed line as possible, according to where the clearest points of the muscle borders could be identified.

All measurements were taken in centimetres (cm) with an accuracy of up to 2 decimal places.

Justification of Scanning Point

Although there is no clear evidence to indicate where in the quadriceps muscle hypertrophy is most likely to occur, the mid-point has shown change in previous research (Abe et al. 2000). Standard distance measurement of 10-15 cm superior to patella has been widely used (Bemben 2002, O'Sullivan et al. 2009). However, using a standard fraction of leg length is preferable as the same portion of the muscle will be measured between participants. Fractions of muscle length have been used previously in the measurement of the quadriceps muscle (Seymour et al. 2009, Walton et al. 1997).

Pilot of Protocol

The measurement protocol was piloted on five healthy adults, who were tested at the same time of day a minimum of 3 days apart. The results are outlined in **Table 8**. The statistical testing was carried out using the Predictive Analytics SoftWare (PASW) package version 18.0 from Statistical Package for Social Sciences (SPSS).

Table 8 Reliability of Pilot Ultrasound Measurement

Muscle	ICC	95% (CI) of the ICC	Range of Mean Diffs as % of Muscle Thickness (Day 1)
Rectus Femoris	0.911	0.382 – 0.990	1.1 – 10.3
Vastus Intermedius	0.848	0.116 – 0.983	0.6 – 26.5

ICC: Intra-Class Correlations; **CI:** Confidence Interval; **Diffs:** Differences

The high ICC values indicate high reliability for the measurement of both muscles. However, the 95% CI of the ICCs and the range of mean differences as a percentage of muscle thickness were wide, indicating inconsistency in measurement. The relative inexperience of the blinded assessor in taking these types of measurements and the small number of participants may explain this variability in measurement. It was recognised that with increased practice prior

to testing, measurement error would be reduced. Therefore, this protocol was deemed suitable.

Spasticity

The Modified Ashworth Scale (MAS) and the Tardieu Scale are commonly used objective clinical measures of spasticity. A review of the MAS has demonstrated that its psychometric properties are poor (Pandyan et al. 1999). Similar findings were made in a review of the psychometric properties of the Tardieu Scale (Haugh et al. 2006). Therefore, a subjective measure of spasticity appeared to be more appropriate.

The Multiple Sclerosis Spasticity Scale – 88 is an 88 item questionnaire on the effect of spasticity on the daily life of PwMS. Although this measure has been shown to be valid and reliable (Hobart et al. 2006), it was not considered appropriate for this study due to the time and energy requirements when other more important measures were to be completed. Therefore, a 10 cm visual analogue scale (VAS) asking how much lower limb spasticity affected the person’s daily activities was used. The VAS used the descriptors “Activities not affected at all”, and “Activities severely affected”, with the numbers 0 and 10 at the respective ends. Although a VAS has not been used previously to evaluate spasticity in an MS population, they have been used widely for pain assessment in numerous populations and have been shown to be valid and reliable (Jensen et al. 1999). Therefore, for the purposes of this study the VAS was considered acceptable. Following initiation of the study, subsequent reading revealed that a similar 0-10 numerical rating scale, was demonstrated to be valid and reliable in an MS population for the evaluation of spasticity (Farrar et al. 2008). In retrospect, this would have been a preferable tool to use, as the psychometric properties of the VAS used are untested.

When printing the VAS, an error was made, resulting in a 10.8 cm line. All values were transformed to represent a 10cm scale using the formula:

$$100 * \frac{\text{original score (mm)}}{108}$$

3.7.2 Activity Outcome Measures

Balance

The Berg Balance Scale

The Berg Balance Scale (BBS) is a standardised outcome measure used in physiotherapy clinical practice with people at risk of falling. The BBS consists of 14 functional tasks that test the static and dynamic components of balance. Performance is rated on a 0 (cannot perform) to 4 (normal performance) nominal scale.

The BBS has been demonstrated to have acceptable concurrent validity in PwMS (Cattaneo et al. 2006). These authors found that the BBS has high specificity but low sensitivity (90% and 40% respectively). The intra- and inter-rater reliability of the BBS was found to be superior to three other balance scales with the highest ICCs and smallest mean differences (Cattaneo et al. 2007). Therefore, the BBS was considered an appropriate scale for evaluating balance.

Mobility

Timed Up and Go

The Timed Up and Go test (TUG) is a timed measure of mobility that involves standing-up, walking 3 m, turning around, walking back and sitting down at a forced speed (quickly but safely). Numerous MS studies that have evaluated mobility following an exercise intervention have used the 6-minute and 10 m walk tests (Rampello et al. 2007, Van den Berg et al. 2006, Lord et al. 1998). However, since mobility was being assessed in the home setting the availability of 10 m walkways to perform these tests was likely to be limited. The TUG was considered a suitable alternative on this basis. In addition, the validity of the TUG for measuring functional mobility in an elderly population has been previously established (Podsiadlo and Richardson 1991) and it has demonstrated high reproducibility in an MS population (Nilsagard et al. 2007).

Multiple Sclerosis Walking Scale – 12

An additional measure of mobility is recommended by Nunnally and Bernstein (1994) (cited in Hobart et al. 2003), on the basis that when evaluating complex

motor activity such as walking, the use of objective and subjective measures is superior to objective measures only. The Multiple Sclerosis Walking Scale (MSWS -12) is a 12 question scale that evaluates the effects of the person's MS status on their ability to mobilize on a daily basis. Each question is rated on a 5 point ordinal scale (1-5) with a descriptor for each point on the severity of mobility impairment due to their MS.

The MSWS-12 has been demonstrated to have good convergent validity with the EDSS and the MSIS-29 physical sub-scale and excellent responsiveness to change (McGuigan and Hutchinson 2004). The scale has also been validated against physical activity measured with an accelerometer (Motl and Snook 2008). The test-retest reproducibility of the MSWS-12 has been shown to be good (Hobart et al. 2003).

3.7.3 Participation Outcome Measures

Quality of Life

Multiple Sclerosis Impact Scale –29 (version 2)

The Multiple Sclerosis Impact Scale (MSIS-29) is a health related quality of life (HRQoL) questionnaire that has been specifically developed for the MS population. The original MSIS-29 consisted of 29 questions rated on a 5 point ordinal scale (1-5), and contained a physical and psychological subscale. The descriptor for each point describes how limited the aspect of HRQoL is due to MS. A recent Rasch analysis (Hobart and Cano 2009), has determined that the scale should be refined to a 4 point ordinal scale to adequately fit the constructs of each subscale (MSIS-29v2). A Rasch analysis determines whether adding the scores of the scale and subscale are justified, based on the fit between the data and the model. This type of analysis also satisfies the 5 conditions required to evaluate the psychometric robustness of a rating scale (Hobart and Cano 2009). Therefore the MSIS-29 is considered to be the best suited HRQoL measure for PwMS.

The MSIS-29 physical subscale was calculated by adding the scores for questions 1 to 20. For the psychological subscale questions 21 to 29 were

summed. Due to the design of the scale the lowest score for the subscales cannot be 0, therefore it is recommended (Hobart and Cano 2009) that scores for the subscales are transformed to a scale of 0-100 using the following formula:

$$100 * \frac{(\text{observed score} - \text{minimum score})}{(\text{maximum score} - \text{minimum score})}$$

A higher score indicates greater impact of MS on HRQoL. The total score is also reported and analysed to allow comparison with the outcomes from other literature.

Fatigue

Modified Fatigue Impact Scale

The Modified Fatigue Impact Scale (MFIS) is a 21 item questionnaire that has been recommended by the National Multiple Sclerosis Society (1998) for use in clinical practice and research. The MFIS is rated on a 4 point ordinal scale (1-4), with a descriptor of the perceived impact of fatigue on daily activities. The MFIS score is calculated by summing the score for the 21 questions. A higher score indicates a greater impact of fatigue.

The MFIS has been validated against the Fatigue Severity Scale (Tellez et al. 2005). According to these authors, the MFIS is a better measure of fatigue due to its multi-dimensionality, with physical, cognitive and social components. In addition, the MFIS has demonstrated moderate to excellent reproducibility in four different European populations of PwMS (Kos et al. 2005).

3.7.4 Order of Outcome Measure Testing

The order of the outcome measures was standardised. The purpose of this was to ensure that any effects that one outcome measure may have on another was consistent between participants. The ordering of the outcome measures was primarily based on providing participants with a rest between measures requiring physical activity. This was deemed necessary as increased fatigue is recognised as an issue for PwMS following physical activity or exercise (Freal et al. 1984).

The order was:

1. Quadriceps Thickness
2. The Modified Fatigue Impact Scale
3. Hand-held Dynamometry
4. The Multiple Sclerosis Walking Scale - 12
5. The Berg Balance Scale
6. The Multiple Sclerosis Impact Scale – 29
7. The Timed Up and Go Test
8. Lower Limb Spasticity
9. Quadriceps Endurance

3.8 Data Management

Strength Data Normalization

The strength data were normalized, as is common practice in research. All baseline values were changed to a value of 100 and the data for the second and third time points was transformed using the following formula:

$$\text{Mid-Intervention} = (\text{Mid-Intervention Score} / \text{Pre-Intervention Score}) * 100$$

$$\text{Post-Intervention} = (\text{Post-Intervention Score} / \text{Pre-Intervention Score}) * 100$$

Change Score

For the purpose of the between group analysis, a change score was calculated for each outcome measure and each intervention period using the following formulae:

$$\text{Change 1} = \text{Week 6} - \text{Week 0}$$

$$\text{Change 2} = \text{Week 12} - \text{Week 6}$$

$$\text{Change 3} = \text{Week 12} - \text{Week 0}$$

Exercise Diary Variables

In order to investigate whether there were any difference between groups in the quantity of exercise they completed, the following variables were calculated for the intervention periods.

- Number of total and quadriceps repetitions completed
- Total and quadriceps work completed. Work was defined as “Weight + Repetition”. It was necessary to use this definition instead of “Weight x Repetitions”, as some participants used 0.5 and 1 kilogram. Therefore, multiplication of weight by repetitions would under-represent the work done in some instances.
- Number of session completed

3.9 Sample size

The calculation of an adequate sample size, powered to detect a significant change in the primary outcome (strength), could not be performed, as effect sizes for the Kneehab device have not been determined previously. On this basis, the study statistician (statistical consulting unit U.L.) advised recruitment of as many participants as possible within the time limitations of the study. In previous resistance training studies for PwMS sample sizes ranged from 5-95. Therefore, a sample size of 35-40 was considered adequate due to the preliminary nature of the investigation and was deemed suitable within the available timeframe.

Chapter 4 – Clinical Profile of People with MS that Use a Walking Aid

4.1 Introduction

A clinical profile, from a physiotherapy perspective, describes the demographics, clinical problems and the associations between these problems. In previous studies investigating the main clinical problems and severity of these problems in PwMS, the cohorts were heterogeneous in terms of disability (Coote et al. 2010, Wu et al. 2007, Khan et al. 2006, Paltamaa et al. 2006). Although Khan et al. (2006) sub-grouped participants by disability level on the EDSS, no study has evaluated the severity of the main clinical problems in PwMS by mobility level, which is an important predictor for disability (Salter et al. 2009). As a result, the severity of the clinical problems experienced by PwMS who use a walking aid is unclear. Establishing this information is valuable in guiding health professionals in the rehabilitation of main the problems this sub-group experiences.

Reduced muscular strength and endurance are well-recognised impairments in the MS population (Carroll et al. 2005, de Haan et al. 2000). Limitations in function, particularly balance and mobility, are also a considerable problem for PwMS (Coote et al. 2010, Paltamaa et al. 2006). Despite strong links between strength and function in the stroke and older adult populations (Moxley Scarborough et al. 1999, Bean et al. 2002, Weiss et al. 2000, Kobayashi et al. 2011), these relationships are not well established in the MS population, according to the findings in part 1 of the literature review (**Chapter 2**). An understanding of whether these relationships exist in PwMS may also help to guide clinicians in the type of interventions they employ to improve impairment and functional problems simultaneously.

4.2 Aims and Objectives

The primary aim of this chapter is to investigate the clinical profile of PwMS who use a walking aid to mobilise. The objectives were to:

1. Describe the demographic characteristics and the severity of the clinical problems in terms of impairments, activity limitations and participation restrictions.
2. Evaluate associations between the clinical problems.

4.3 Methods

In collecting the baseline data, the methods outlined in **Chapter 3** were followed. The associations between clinical problems outlined in the first section of the literature review (**Chapter 2**) were investigated.

4.3.1 Data Analysis

All statistical testing was carried out using the PASW package version 18.0 from SPSS. Two lower limb extensor strength variables (weak and strong side) were calculated by summing quadriceps, plantar-flexor and gluteal strengths for the respective sides. The baseline measurement values were analysed for normality using the Shapiro-Wilk test, as it is suitable for sample sizes of less than 50 (Riffenburgh 1999). If this value was <0.05 data were deemed to be non-normally distributed. The normality values for the baseline measurements are provided in **Appendix 6**. Data are presented as means (medians) and standard deviations (interquartile range - IQR).

The associations were analysed with correlation tests. If both variables were normally distributed, Pearson's Correlation Coefficient (PCC) was used. If one or both of the variables was non-normally distributed, Spearman's Correlation Coefficient (SCC) was used. The strength of the association was evaluated based on the correlation coefficient value (weak <0.4 ; moderate $0.4 - 0.7$; strong >0.7) (Portney and Watkins 2000), and the p value (significant at $p < 0.05$). Scatter-plots are included to demonstrate the strength of the correlations.

4.4 Results

4.4.1 Demographic Characteristics and Clinical Problems

The demographic characteristics of the study group are outlined in **Table 9**. There were higher percentages of women as compared to men, and people with relapsing remitting MS as opposed to other MS types. The percentage of people using bilateral support to mobilise was 40.5% in the present study.

Table 9 Demographic Characteristics

% of Male / Female	29.7 / 70.3
Mean Age \pm SD, yrs	52.44 \pm 10.87
Mean Time Since Diagnosis \pm SD, yrs	11.34 \pm 4.94
% Type of MS (RR / PP / SP / BN / UnK)	43.2 / 29.7 / 16.2 / 2.7 / 8.1
% Unilateral / Bilateral Support	59.5 / 40.5

SD = Standard Deviation; **RR** = Relapsing Remitting; **PP** = Primary Progressive; **SP** = Secondary Progressive; **BN** = Benign; **UnK** = Unknown

A summary of the descriptive statistics for the normally distributed impairment outcomes is provided in **Table 10**. All measures of strength and muscle thickness demonstrated a high degree of variability. The difference in impairments between the strong and weak side is evident from all of the strength data but not the quadriceps thickness values. One participant exceeded the 220 N maximum limit of the HHD, for quadriceps strength on their strong side.

In **Table 11** the non-normally distributed impairment outcomes are outlined. Nineteen of the 37 participants reported spasticity affecting their lower limbs. The effect of spasticity on participants' daily activities was highly variable. For quadriceps endurance, participants' completed a median of 12 sit-to-stand repetitions. The range in quadriceps endurance values was wide, indicating high variability.

Table 10 Descriptive Statistics Normally Distributed Impairment Outcomes

Outcome Variable	Unit	N=	Mean ± SD	Min – Max
Quadriceps Strength Strong Side	Newtons	37	156.8 ± 40.7	54.3 – 220
Quadriceps Strength Weak Side	Newtons	37	115.9 ± 40.5	50.6 – 217
Plantar-flexor Strength Strong Side	Newtons	37	130.5 ± 45.6	37.4 - 215.3
Plantar-flexor Strength Weak Side	Newtons	37	98.2 ± 48.5	11 – 206.7
Lower Limb Extensor Strength Strong Side	Newtons	37	350.9 ± 97.5	148.2 – 537
Lower Limb Extensor Strength Weak Side	Newtons	37	258.9 ± 98	90.9 – 523.9
Rectus Femoris Thickness Strong Side	Centimetres	35	1.59 ± 0.31	1.02 – 2.19
Rectus Femoris Thickness Weak Side	Centimetres	35	1.54 ± 0.42	0.60 – 2.52
Spasticity	Centimetres	19	4.8 ± 3.1	0.2 – 9.3

SD = Standard Deviation; **n**= number of participants with data available for outcome variable

Table 11 Descriptive Statistics Non-Normally Distributed Impairment Outcomes

Outcome Variable	Unit	n=	Median (IQR)	Min – Max
Gluteal Strength Strong Side	Newtons	37	58.7 (35.9)	22.7 – 123
Gluteal Strength Weak Side	Newtons	37	39.6 (34.1)	8.8 – 113.3
Vastus Intermedius Thickness Strong Side	Centimetres	35	1.23 (0.59)	0.72 – 2.86
Vastus Intermedius Thickness Weak Side	Centimetres	35	1.23 (0.61)	0.61 – 2.83
Total Quadriceps Thickness Strong Side	Centimetres	35	2.83 (0.94)	1.98 – 5.05
Total Quadriceps Thickness Weak Side	Centimetres	35	2.73 (1.16)	1.25 – 5.35
Quadriceps Endurance	Repetitions	37	12.0 (19.5)	0 – 141

IQR = interquartile range; **n**= number of participants with data available for outcome

The descriptive statistics for the activity and participation outcomes are outlined in **Tables 12** and **13**. The level of balance impairment was moderate with the mean of the BBS score (39) in the middle of the scale's range (0-56). The variability in balance level was high in this population. The mean fatigue score of 42.9 was also in the middle of the MFIS 0-84 range, indicating a moderate level of fatigue. Similar to the balance scores the severity of fatigue was highly variable in this group.

Table 12 Descriptive Statistics Normally Distributed Activity and Participation Outcomes

Outcome Variable	Unit	n=	Mean ± SD	Min – Max
Balance (BBS)	Scale (0-56)	37	39 ± 9.5	10 – 53
Fatigue (MFIS total)	Scale (0-84)	35	42.9 ± 15.5	3 – 75
Quality of Life (MSIS-29v2 total)	Transformed Scale (0-100)	36	43.4 ± 21.4	8 – 83.9

SD: Standard Deviation; **n:** number of participants with data available for outcome; **BBS:** Berg Balance Scale; **MFIS:** Modified Fatigue Impact Scale; **MSISv2:** Multiple Sclerosis Impact Scale Version 2

In this cohort, the impact of MS on HRQoL for the total and physical scores was moderate with the mean and median respectively in the middle of the 0-100 range of the scale. The median score on the psychological subscale for HRQoL was 27.8, indicating a low impact of this variable on HRQoL in our group. Variability was high on all the HRQoL scales. For both measures of mobility, the limitations of the participants in this group were moderate to severe, as the median TUG time was 21 seconds and the median MSWS-12 score was 49 out of a maximum of 60. The range of values for both mobility measures was wide, indicating a high level of variability.

Table 13 Non-Normally Distributed Activity and Participation Outcomes

Outcome Variable	Unit	n=	Median (IQR)	Min – Max
Quality of Life (MSIS-29v2 physical)	Transformed Scale (0-100)	37	51.7 (35)	10 – 91.7
Quality of Life (MSIS-29v2 psychological)	Transformed Scale (0-100)	36	27.8 (33.3)	0 – 85.2
Mobility (TUG)	Seconds	37	21.1 (15.1)	9.9 – 85
Mobility (MSWS-12)	Scale (0-60)	37	49 (11.5)	13 – 58

IQR: interquartile range; **n:** number of participants with data available for outcome; **MSISv2:** Multiple Sclerosis Impact Scale Version 2; **TUG:** Timed Up and Go; **MSWS-12:** Multiple Sclerosis Walking Scale-12

4.4.2 Correlations between Impairment and Activity Outcomes

The strength and significance of the correlations between impairments and activity outcomes is detailed in **Table 14**.

Table 14 Correlations between Impairment and Activity Outcomes

Impairment Outcome	Activity Outcome		
	Balance	Mobility (TUG)	Mobility (MSWS-12)
Quadriceps Strength Weak Side	0.200	0.069 †	-0.451** †
Lower Limb Extensor Strength Weak Side	0.336*	-0.222 †	-0.411* †
Quadriceps Endurance	0.692** †	-0.583** †	-0.255 †
Spasticity	0.073	0.031 †	0.355 †

*, ** : significant at $p < 0.05$, $p < 0.001$ respectively for Pearson's correlation coefficient; † : Spearman's correlation coefficient

Significant correlations of moderate strength were seen between; quadriceps strength and mobility (MWSW-12) ($p=0.005$), and lower limb extensor strength and mobility (MSWS-12) ($p=0.011$). Both correlations were negative (**Figure 10** and **11**), indicating that people with more impaired mobility had lower strength. Lower limb extensor strength and balance were significantly ($p=0.042$) but weakly correlated (**Figure 12**). Quadriceps endurance was significantly and moderately correlated with balance ($p < 0.01$) and mobility ($p < 0.01$) on the TUG

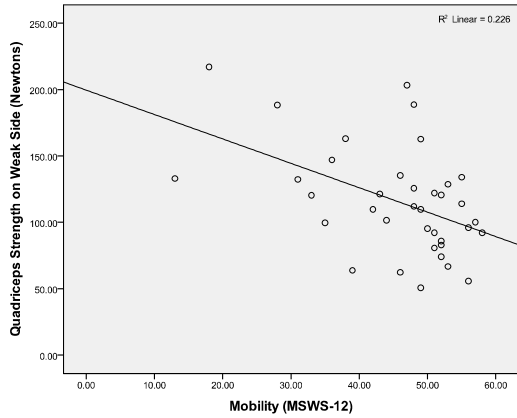


Figure 10 Quadriceps Strength (Weak Side) and Mobility (MSWS-12) ($r = -0.451$)

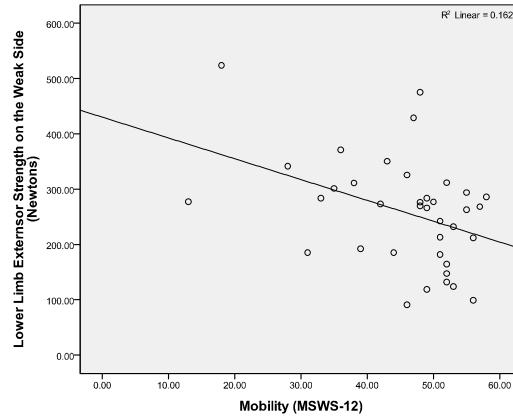


Figure 11 Lower Limb Extensor Strength (Weak Side) and Mobility (MSWS-12) ($r = -0.411$)

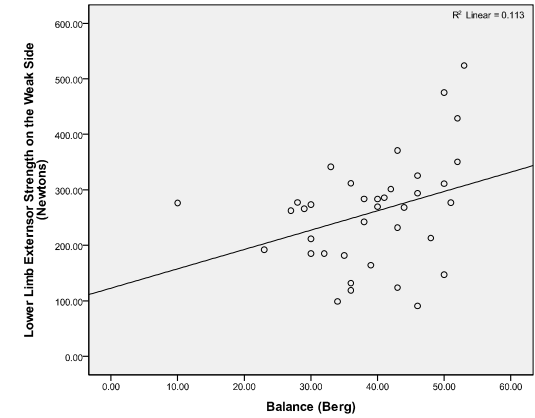


Figure 12 Lower Limb Extensor Strength (Weak Side) and Balance ($r = 0.336$)

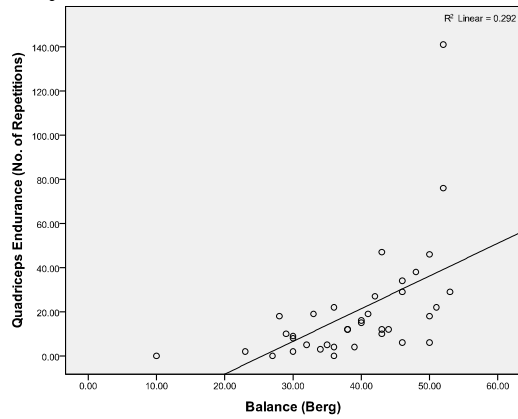


Figure 13 Quadriceps Endurance and Balance ($r = 0.692$)

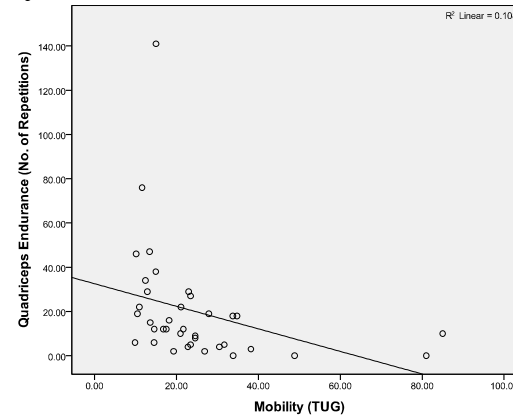


Figure 14 Quadriceps Endurance and Mobility ($r = -0.583$)

(Figure 13 and 14). The correlation between quadriceps endurance and mobility was negative, suggesting that people with greater endurance walked faster.

4.4.3 Correlations between Impairment Outcomes

There was a weak but significant correlation between quadriceps strength and muscle thickness on the weak side ($p=0.046$) and on the strong side ($p=0.031$). The association was such that participants with greater strength had greater quadriceps muscle thickness (Figure 15 and 16).

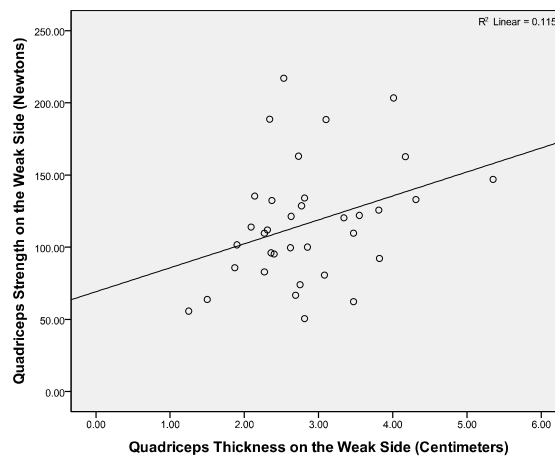


Figure 15 Quadriceps Strength and Thickness on the Weak Side ($r=0.339$)

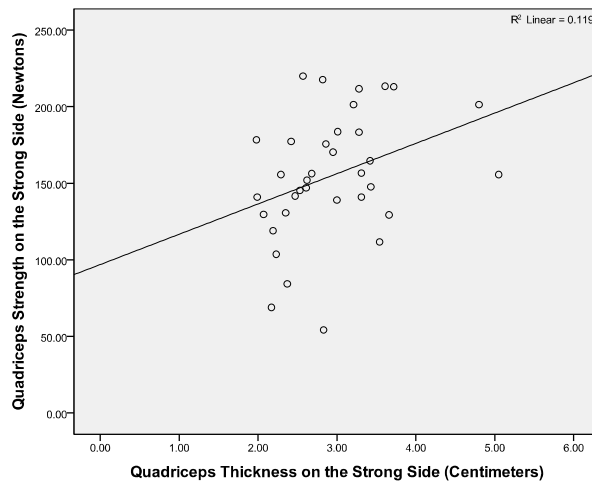


Figure 16 Quadriceps Strength and Thickness on the Strong Side ($r=0.366$)

4.4.4 Correlations between Impairment and Participation Outcomes

There was no correlation between quadriceps endurance and fatigue ($r=0.134$; $p=0.437$).

4.5 Discussion

4.5.1 Demographics and Clinical Problems

In this study, the higher proportion of women and people with relapsing remitting MS was reflective of the demographic profile of the general MS population (Paltamaa et al. 2006, Khan et al. 2006). Bilateral aid was used by 40% of participants in this cohort. Of the participants who used an aid in a large population-based study (Minden et al. 2004), 28.5% required bilateral assistance. This difference in percentage of bilateral aid users suggests that the present population were more disabled. The severity of the clinical problems experienced by this group was highly variable, despite the inclusion of a more defined sub-group in terms of disability. This is indicative of a heterogeneous level of impairment and disability in this cohort.

Presently, there are no comparable muscle strength data, using hand-held dynamometry in other MS populations. However, the knee extension strength values of this group (115.9 N on the weak side and 156.8 N on the strong side) were much lower than for healthy adults aged 70-79 (356.9 N) and people post-stroke (203.9 N) (Bohannon 1997, Cameron and Bohannon 2000). A ceiling effect of the HHD does not appear to have affected this result as only one participant exceeded the upper measurement limit. In addition, the considerable asymmetry in leg strength between the strong and weak sides substantiates the results of two previous studies (Chung et al. 2008, Broekmans et al. 2011). This supports the view that MS impairments are primarily unilateral in presentation, and thus rehabilitation should be targeted to the more impaired side.

In terms of function, balance in this cohort (39 on the BBS) was more impaired than people with Parkinson's Disease (46) or a moderate to severe stroke (44) (Brusse et al. 2005, Smith et al. 2004). Similarly, the balance of participants in the present study was more limited than individuals with MS in another study, who had a mean BBS score of 46 (Nilsagård et al. 2009b). The participants in the Nilsagard et al. (2009b) study were classified as fallers and were less disabled, according to their EDSS score of 3.5 to 6, than our cohort. This

suggests that the participants in our study were at equal or greater risk of falls than less disabled PwMS, considering their higher level of balance impairment. Furthermore, in our participants the median time to mobilise 3 m on the TUG test (21.1 seconds) was the same as institutionalised elderly women, and substantially slower than elderly community dwelling women (8 seconds) (Bischoff et al. 2003). People with MS with moderate to mild disability (EDSS of 3 to 6), completed the TUG test in 13.9 seconds (Créange et al. 2007). Participants in the Créange et al. (2007) study rated their impression of mobility impairment on the MSWS-12 at 38, which was less than the 49 reported by participants in the present study. The comparison of these data supports the view that PwMS who use a walking aid experience higher levels of impairment in their mobility compared to other less disabled PwMS and older adults.

These data substantiates the subjective reports of the primary problems experienced by PwMS. Balance and walking difficulties were rated in the top 3 problems in two studies (Coote et al. 2010, Paltamaa et al. 2006), while muscle weakness is widely acknowledged as being a common debilitating problem for PwMS. Furthermore, these data provide empirical support for the clinical impression that PwMS who use a walking aid require a strong rehabilitation emphasis on improving balance, mobility and muscle strength.

The subjective fatigue experienced by the participants in our study was 42.9 on the MFIS, which suggests a moderate level of fatigue considering the range of the scale is 0-84. In a large population-based study of fatigue levels in PwMS, respondents who used a walking aid reported their fatigue to be 45 to 50 on the MFIS (Hadjimichael et al. 2008). A similar MFIS score was reported in a moderately disabled population of PwMS (EDSS mean = 5.2) (Hugos et al. 2010). Therefore, the fatigue data for our participants support the view that PwMS who use a walking aid experience moderate levels of fatigue. Similarly there was a moderate level of restriction in HRQoL for the participants in our study. The total and physical subscale scores for the MSIS-29v2 were in the middle of the 0 to 100 range of the transformed scale. The psychological subscale score of 27.3 indicates a mild level of restriction in this HRQoL domain. Presently, comparable data in other MS populations is not available for

version 2 of the MSIS-29. Therefore, these preliminary data suggest that PwMS who use a walking aid experience greater physical, rather than psychological, restrictions in HRQoL.

For spasticity, 19 (51.4%) of participants reported experiencing this as a problem. According to the NARCOMS registry, 84% of PwMS experience symptoms of spasticity (Rizzo et al. 2004). This indicates that the prevalence of this symptom was less in our participants compared to the general MS population. However, this conclusion is compromised by the fact that participants were asked to rate how much spasticity impacted upon their ADL, rather than whether they experienced spasticity. Thus, the prevalence of spasticity in our group may be under-represented. Nonetheless, the median spasticity severity rating of 4.8 cm on the VAS in our participants was lower than the 6.95 cm reported in a large cohort of PwMS (Wade et al. 2006). Although this may be due to a difference in disability levels, Wade et al. (2006) did not clearly report the disability of their cohort. Thus, further investigation is required to determine the severity of spasticity in PwMS who use a walking aid.

The novel nature of the measures used to evaluate quadriceps thickness and endurance preclude direct comparison to other populations including MS. Nonetheless, the severity of the muscle weakness in the present cohort suggests that reduced quadriceps thickness is a problem for PwMS who use a walking aid. This contention is supported by the association between muscle strength and CSA that has been established in PwMS (Kent-Braun et al. 1997, Ng et al. 2004). Furthermore, a high level of muscle endurance impairment in the present population is substantiated by the findings of Sharma et al. (1995) and de Haan et al. (2000). In both studies, quadriceps and tibialis anterior endurance was significantly reduced in PwMS who did and did not use a walking aid compared to healthy adults. Therefore, although both quadriceps thickness and endurance appear to be major problems for PwMS who use a walking aid, this assertion needs to be substantiated in future studies using standardised outcome measures and methods, such as MRI and repeated knee extensions on an IKD.

4.5.2 Associations Between Clinical Problems

The second objective in determining the clinical profile of PwMS who use a walking aid was to evaluate the associations between the clinical problems. Overall, the strength of the associations between the clinical problems was mixed. The variables of quadriceps endurance and balance, and quadriceps endurance and mobility (TUG), were significantly and moderately correlated. The other associations demonstrated moderate or weak correlations.

The strength of the correlations between quadriceps endurance and balance, and quadriceps endurance and mobility, suggest a clinically significant association between these variables. However, in order to determine the clinical significance of the correlation, the nature of the tests needs to be considered. Sit-to-stand (STS) was a common activity between the quadriceps endurance, balance and mobility tests. Therefore, the association may be due to the ability of participants to complete a STS effectively or with minimal effort, rather than an association between the different variables they measure. This argument is supported by the fact that the STS action requires a certain level of strength, coordination and balance (Eriksrud and Bohannon 2003, Lord et al. 2002). Consequently, since the repeated STS outcome did not measure quadriceps endurance exclusively, the strength of the actual associations between quadriceps endurance and both balance and mobility are limited. Furthermore, the association between quadriceps endurance and mobility is not well supported theoretically, as the mobility test evaluated speed rather than endurance. Although neither of these associations have previously been investigated in the MS population, the present results do not fully support a relationship existing between the variables. This is primarily due to the issues with the similar nature of the tests, the use of tests which do not measure the intended variable, and the weak ability of correlation tests to determine a causal relationship. Further investigation is warranted, as the presence of a relationship between these problems would support the use of an endurance training programme to improve balance and mobility.

The moderate correlations between isometric muscle strength and self-rated mobility (MSWS-12) suggest that due to greater muscle weakness participants

perceived a higher level of mobility impairment. However, this was not substantiated in the correlations between isometric strength and the objective measure of mobility (TUG). Similarly, there were weak associations between isometric strength and balance. The lack of an association between these variables was unexpected, based on the findings of Kobayashi et al. (2011). Kobayashi et al. (2011) found moderate to strong associations between isometric quadriceps strength (using HHD and the same measurement method as the present study) and mobility on the TUG, and balance on the BBS, in people who had experienced a stroke. This suggests that differences between the stroke and MS populations may be the reason for the absence of the associations in this group of PwMS. A possible explanation may be the inconsistencies in muscle activation in our cohort, which may have affected accurate strength evaluation. This may have similarly affected the weak relationship between quadriceps strength and thickness. Another issue may be that the HHD used could not measure strength above 220N. As a result, strength may have been underestimated in some participants, leading to a weaker association between strength and functional or muscle thickness measures. The lack of association between the measure of spasticity and the functional outcomes may be explained by the fact that perceived spasticity, rather than objective spasticity, was evaluated.

4.5.3 Limitations

The primary limitations in this study are the small sample and variability in severity of clinical problems. Both of these issues reduce the generalisability of the results to the wider population of PwMS who use a walking aid. The measurement of the clinical problems may also have been affected by the quality of some of the measures, which were not the gold standard due to cost and the logistics of implementing them in the home setting. As a result, the internal validity may have been affected. Future studies should employ a lab-based approach, which would allow for the use of validated outcome measures, particularly for strength and muscle endurance.

4.6 Conclusion

People with MS that use a walking aid face a number of clinical problems that result in serious impairment, particularly muscle weakness, balance and mobility. This highlights the need for further intervention to improve these problems. However, to gain a clearer picture of the rehabilitation needs of this population, further sub-grouping by disability level is necessary. This would reduce the variability in clinical presentation, resulting in more homogenous sub-groups, whose specific intervention needs can be identified. Finally, the present study failed to demonstrate strong associations between many of the clinical problems which have been shown in other populations (**Chapter 2**). This is an important area for future studies to focus on, in order to establish whether relationships between certain clinical problems exist. Understanding the nature of any relationships may inform rehabilitation strategies to improve outcomes and progressions in disability that can be expected, due to a change in an impairment, activity or participation variable.

CHAPTER 5 – EFFECTS OF SUPERIMPOSING NMES ON A PRT PROGRAMME FOR PWMS

5.1 Introduction

This chapter outlines the results and discusses the clinical implications of the main study comparing the effects of a home-based PRT programme to the same programme with the Kneehab device.

In the literature review (**Chapter 2**), PRT was shown to improve outcomes in the domains of impairment (particularly strength), activity limitation and participation restriction in PwMS. Strength gains have been highlighted as important in stroke rehabilitation, due to associations with improved function (Ada et al. 2006). On this basis, Ada et al. (2006) advocated the need for future research to prioritise the investigation of effective ways to increase strength. In neurological populations NMES is an effective strategy for increasing strength (Glinsky et al. 2007, Sheffler and Chae 2007). The systematic review by Glinsky et al. (2007) recommended superimposing NMES on voluntary contraction. Although this has been evaluated in PwMS (Livesley 1992, Wahls et al. 2010, Broekmans et al. 2011), limited effects were seen and the methodological quality of the studies was generally low. Consequently, there are two main gaps in the literature. First, it is unclear whether superimposing NMES on PRT results in positive treatment effects for PwMS. The second unanswered question is whether adding an NMES device to a PRT programme improves outcomes compared to PRT alone.

From a health service delivery perspective, it is important to know the length of rehabilitation required to achieve treatment effects that are clinically meaningful. Therefore, by evaluating outcomes in the groups at different intervention lengths, the optimal length of rehabilitation with PRT or NMES can be identified.

Finally, there is increasing literature suggesting that the addition of a device to an exercise intervention increases intervention participation. A recent systematic review found that physical activity is increased when a pedometer is added to the intervention (Bravata et al. 2007). Similarly, increased exercise participation has been shown when a treadmill is added to a home-based aerobic exercise programme (Jakicic et al. 1999). To this author's knowledge, this effect has not been evaluated using an NMES device. Therefore, an evaluation of this effect is important as it may result in increased intervention and subsequently improved outcomes.

5.2 Aims and Objectives

In the first part of this chapter, the flow of participants through the study, the incidence of participants' group allocation being revealed to the assessor, baseline differences between groups and the powering for the main outcome measure will be outlined.

The second part of the chapter aims to answer the question, "What are the clinical effects of adding the Kneehab device to a PRT programme for PwMS?"

The objectives were:

1. To determine if the PRT and Kneehab groups were similar at baseline.
2. To evaluate:
 - a. whether there were treatment effects within the groups.
 - b. during which intervention period (0-6, 6-12 or 0-12 weeks) the treatment effects occurred in the groups.
3. To compare the differences in treatment effect between the groups.
4. To compare the intervention participation between the groups.

5.3 Methods

The methods outlined in **Chapter 3** were followed.

5.3.1 Data Analysis

A post-hoc test to determine the sample sizes required to detect a significant within group difference with 80% power using nQuery Advisor was performed for the primary outcome measure (quadriceps strength). All other statistical testing was carried out using the PASW package version 18.0 from SPSS. Outcomes at all time points for both groups were analysed for normality using the Shapiro-Wilk test and normality plots as described previously. A summary of all normality values is provided in **Appendix 7**. For all tests comparing outcomes within and between groups, a p-value of <0.05 indicated a significant difference.

Analysis for Objective 1

Independent T-Tests (normally distributed outcomes) and Mann-Whitney U tests (non-normally distributed outcomes) were performed to determine whether groups were different at baseline. For the Independent T-Test, Levene's test indicated whether the "equal variances assumed" ($p>0.05$) or "equal variances not assumed" ($p<0.05$) p-value was appropriate. An example of the PASW output and the p-values for the difference between groups are provided in **Appendix 8**.

Analysis for Objective 2a

A one-way repeated measures analysis of variance (ANOVA) was performed on normally distributed data to determine if there was a significant within-group treatment effect. If the p-value for Mauchly's test of Sphericity was >0.05 the Sphericity Assumed value was used; if this value was <0.05 , the Greenhouse-Geisser value was used to indicate the within-group treatment effect. The non-normally distributed data were analysed for within group treatment effects using Friedman's ANOVA. The 2-tailed exact significance p-value was used to indicate if a significant effect occurred.

Analysis for Objective 2b

To determine during which intervention period treatment effects occurred, a post-hoc analysis with Bonferroni correction was performed on the normally distributed outcomes. A Wilcoxon-Signed Ranks Test was performed for each

intervention period on the non-normally distributed outcomes. (See **Appendix 9** for an example of within-group analysis outputs).

Analysis for Objective 3

In order to evaluate if there was a significant difference in outcomes between groups, the change score variable was used. A one-way repeated measures ANOVA with a between-groups factor of group allocation was performed on normally distributed data. The p-value of the between-subjects effects was used to indicate whether a difference in treatment effect between groups occurred. A similar analysis is not feasible for non-normally distributed data. A post-hoc analysis of between-group differences for the intervention periods was performed using an Independent T-Test or Mann-Whitney U test as described previously. (See **Appendix 10** for an example of the output).

Analysis for Objective 4

To determine if there was a difference in the volume of exercise completed between groups, the exercise diary variables (**Chapter 3 – Data Management**) were examined using an Independent T-Test or Mann-Whitney U test as described previously.

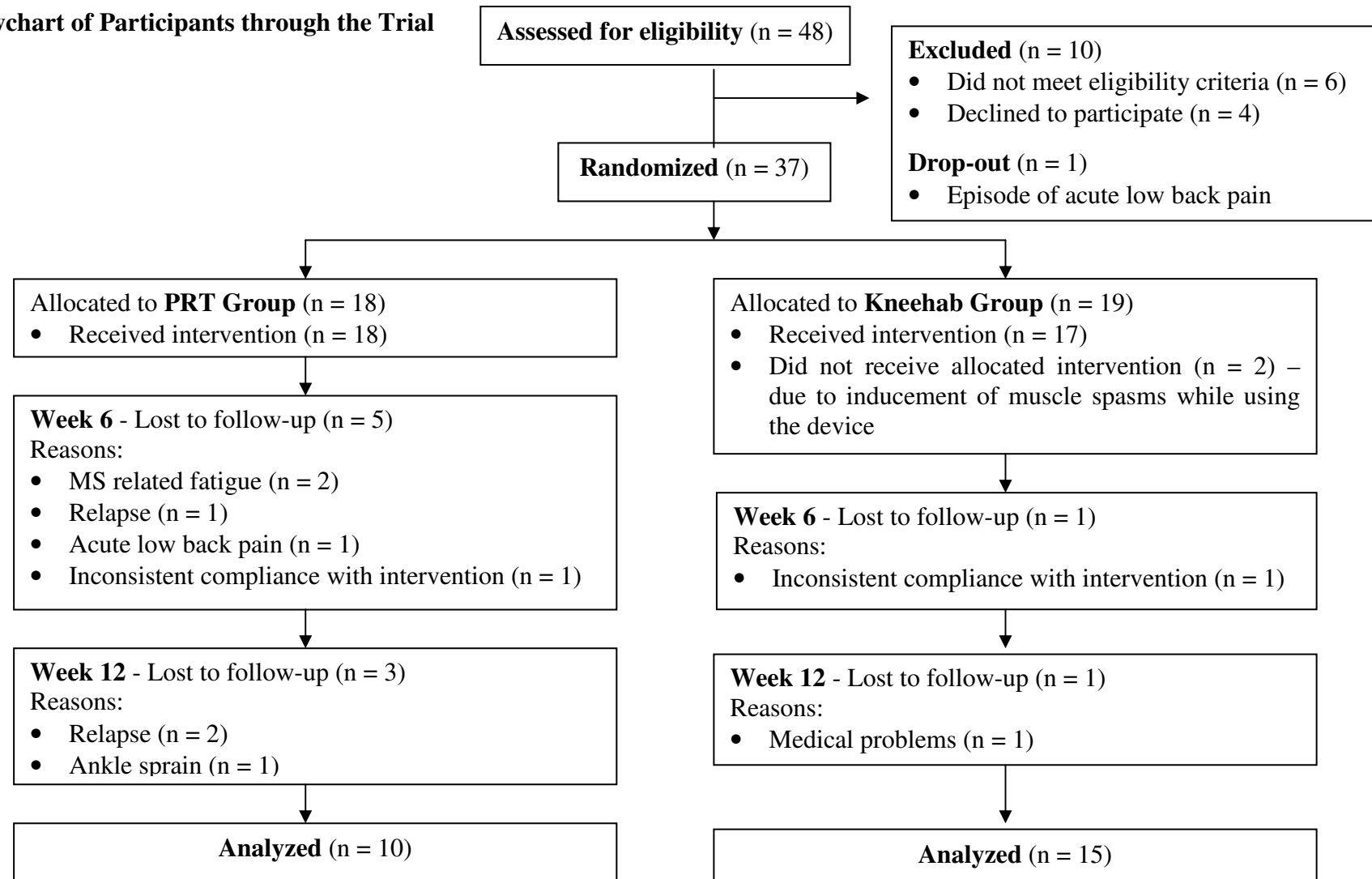
For all analyses descriptive statistics are presented and examined to inform the clinical and statistical significance of any treatment effects.

5.4 Results

5.4.1 Flow of Participants and Blinding

The flow of participants through the trial is described in **Figure 17**. Thirty-seven volunteers were recruited and randomized to the respective interventions. The loss to follow-up was 44.4% in the PRT group and 21.1% in the Kneehab group. Two participants in the Kneehab group experienced the same adverse event where strong muscle spasm was induced in surrounding muscles during stimulation. The Kneehab intervention was discontinued with these participants.

Figure 17 Flowchart of Participants through the Trial



Only participants that completed the entire intervention were included in the analysis, regardless of whether their group allocation was revealed. One participant in the PRT group and 2 participants in the Kneehab group revealed their group allocation to the assessor.

5.4.2 Group Differences at Baseline

The baseline demographic profile of the groups as they were analysed following completion of the study is described in **Table 15**. There was a small difference between the groups in gender balance and proportion of participants with a progressive type of MS. The proportion of participants using unilateral or bilateral support was similar between the groups.

Table 15 Baseline Demographic Profile of Groups Post-Randomization

Demographic Characteristics	PRT Group (n=10)	Kneehab Group (n=15)
% of Male / Female	40 / 60	26.7 / 73.3
Mean Age \pm SD, yrs	51.8 \pm 12.1	51.8 \pm 12.6
Mean Time Since Diagnosis \pm SD, yrs	12.2 \pm 4	11.8 \pm 5.5
% Type of MS (RR / PP / SP / BN / UnK)	40 / 30 / 20 / 0 / 10	53.3 / 26.6 / 6.7 / 6.7 / 6.7
% Unilateral / Bilateral Support	50 / 50	53.3 / 46.7

SD = Standard Deviation; **RR** = Relapsing Remitting; **PP** = Primary Progressive; **SP** = Secondary Progressive; **BN** = Benign; **UnK** = Unknown

In **Table 16** and **17** the baseline differences between the groups for all outcome measures are detailed. There were no statistically significant differences between the groups. There was a trend for the Kneehab group to have higher isometric strength and quadriceps endurance, and worse scores for HRQoL and fatigue than the PRT group.

Table 16 Baseline Differences Between Groups for Normally Distributed Outcomes

Outcome Measure	Unit	Mean (SD)		p-value
		PRT Group	Kneehab Group	
Quadriceps Strength Impaired Side	Newtons	108.3 (± 44.2)	132.3 (± 44.2)	0.198
Plantar-flexor Strength Impaired Side	Newtons	101 (± 49.2)	106.5 (± 56.1)	0.805
Gluteal Strength Impaired Side	Newtons	37.3 (± 15.1)	49.5 (± 30.8)	0.204
Rectus Femoris Thickness Impaired Side	Centimetres	1.74 (± 0.42)	1.54 (± .40)	0.231

SD: Standard Deviation

Table 17 Baseline Differences Between Groups for Non-Normally Distributed Outcomes

Outcome Measure	Unit	Median (IQR)		p-value
		PRT Group	Kneehab Group	
Vastus Intermedius Thickness Impaired Side	Centimetres	1.28 (1.09)	1.23 (0.49)	0.194
Quadriceps Endurance	Repetitions	12 (33.3)	18 (17)	0.775
Spasticity	Centimetres	35.2 (46.8)	39.6 (80.8)	0.672
Balance (BBS)	BBS Score	38.5 (14.3)	40 (17)	0.819
Mobility (TUG)	Seconds	20.2 (11.2)	21.2 (21.9)	0.849
Mobility (MSWS-12)	MSWS-12 Score	49.9 (11.8)	48 (17)	0.373
Quality of Life (MSIS-29v2 Total)	MSIS-29v2 Score	33.3 (33.6)	41.4 (39.1)	0.806
Quality of Life (MSIS-29v2 physical)	MSIS-29v2 Score	42.5 (38.3)	50 (43.3)	0.493
Quality of Life (MSIS-29v2 psychological)	MSIS-29v2 Score	20.4 (25)	25.9 (33.3)	0.662
Fatigue (MFIS Total)	MFIS Score	40 (33.5)	45 (22.3)	0.522

IQR: Interquartile range

5.4.3 Post-Hoc Power Calculations

A sample size of 38 in the PRT group and 36 in the Kneehab group, would be required to detect a significant within-group difference, with 80% power for quadriceps strength.

5.4.4 Treatment Effect for Impairment Outcomes

All strength and RF thickness data were normally distributed. Vastus intermedius thickness, spasticity and quadriceps endurance data were non-normally distributed (**Appendix 7**).

Quadriceps Strength – Impaired Side

In **Table 18** the descriptive statistics and within-group treatment effect for quadriceps strength are presented. The Kneehab group's strength was 24 N higher at baseline. In both groups, strength was highly variable and increased from 0-12 weeks. There was no significant treatment effect in either group. One participant in the PRT group exceeded the maximum measurement of 220 N at the week 6 evaluation.

Table 18 Descriptive Statistics and Within Group Treatment Effect for Quadriceps Strength (Newtons) – Impaired Side

Group	Mean (Standard Deviation)			Repeated Measures ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	108.3 (± 44.2)	114 (± 48.6)	119.7 (± 46.6)	0.393
Kneehab (n=15)	132.3 (± 44.5)	141.7 (± 44)	142.3 (± 44.3)	0.128

Mean (SD): Newtons

In both groups, the within-group treatment effect was non-significant throughout (**Table 19**). There was high variability in the change, with the 95% confidence interval (CI) passing through zero. The strength increase in the PRT group was similar from 0-6 and 6-12 weeks. In the Kneehab group, strength increases occurred from 0-6 weeks, primarily. The inter-individual change in strength was highly variable in both groups (**Appendix 11**).

Table 19 Post-Hoc Analysis of Within Group Treatment Effects for Quadriceps Strength (Newtons) – Impaired Side

Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	\bar{d} (95% CI)	p-value	\bar{d} (95% CI)	p-value	\bar{d} (95% CI)	p-value
PRT (n=10)	5.8 (-27.6 to 39.1)	1.00	5.6 (-11.3 to 22.5)	1.00	11.4 (-11.2 to 34)	0.521
Kneehab (n=15)	9.4 (-6.7 to 25.4)	0.404	0.6 (-12 to 13.2)	1.00	10 (-4.6 to 24.6)	0.251

95% CI: 95% Confidence Interval; \bar{d} : Mean Difference (Newtons)

The difference in treatment effect between groups for quadriceps strength was non-significant during the intervention (**Table 20**). The groups demonstrated a similar treatment effect (**Figure 18**).

Table 20 Between Group Treatment Effects for Quadriceps Strength (Newtons) – Impaired Side

Repeated Measures of ANOVA (p-value)	Post-Hoc Analysis (p-value)		
	0-6 Weeks	6-12 Weeks	0-12 Weeks
0.880	0.760	0.504	0.880

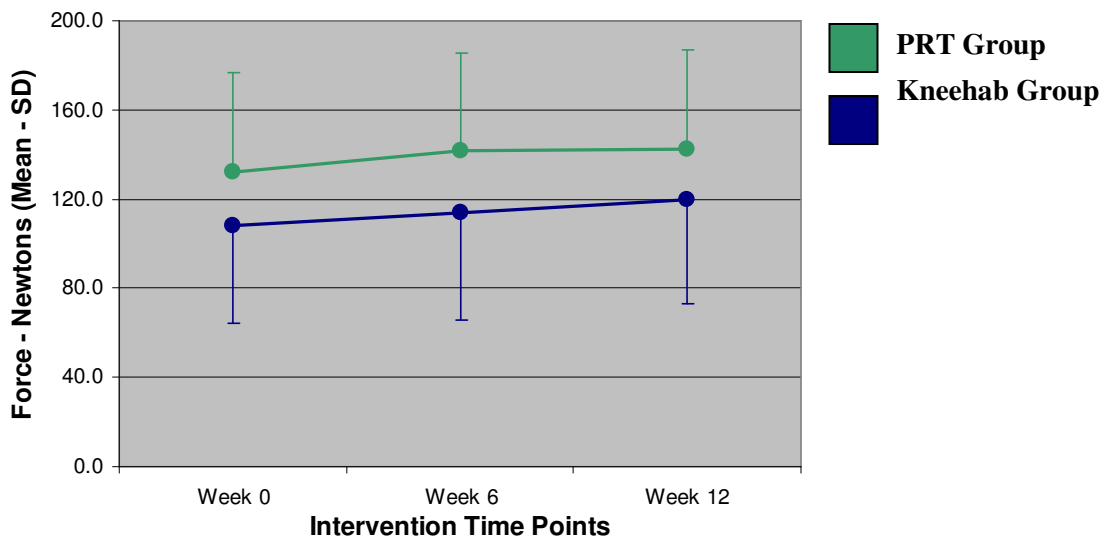


Figure 18 Group Treatment Effects– Quadriceps Strength

Normalized Strength Data

All normalized data for strength demonstrated similar change and within- and between-group significance to the non-normalized data (**Appendix 12**).

Plantar-Flexor Strength – Impaired Side

The groups had similar plantar-flexion strength at baseline (**Table 21**). Both groups demonstrated high variability in strength throughout the intervention. From 0-6 weeks, both groups' strength decreased by close to 19 N. There was an increase of 34 N in the Kneehab group from 6-12 weeks, which was double the increase of the PRT group. There was a significant treatment effect in the Kneehab group. No participants exceeded the 220 N measurement at any time point.

Table 21 Descriptive Statistics and Within Group Treatment Effect for Plantar-Flexor Strength (Newtons) – Impaired Side

Group	Mean (Standard Deviation)			Repeated Measures ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	101 (± 49.2)	82.6 (± 38.1)	99.4 (± 44.1)	0.150
Kneehab (n=15)	106.5 (± 56.1)	87.2 (± 30.8)	121 (± 26.3)	0.016*

Mean (SD): Newtons; *: significant at p<0.05

The post-hoc analysis demonstrated that the decrease in plantar-flexion strength from 0-6 weeks was non-significant in both groups (**Table 22**). The increase in strength in both groups from 6-12 weeks was significant. This increase resulted in a higher strength in the Kneehab group for the 0-12 week intervention period, but no change for the PRT group. The strength changes were consistent in both groups (**Appendix 11**).

Table 22 Post-Hoc Analysis of Within Group Treatment Effect for Plantar-Flexor Strength (Newtons) – Impaired Side

Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	\bar{d} (95% CI)	p-value	\bar{d} (95% CI)	p-value	\bar{d} (95% CI)	p-value
PRT (n=10)	-18.4 (-54 to 17.1)	0.489	16.8 (2.2 to 31.4)	0.025*	-1.6 (-29.7 to 26.5)	1.00
Kneehab (n=15)	-19.3 (-43 to 4.4)	0.133	33.8 (18.4 to 49.2)	<0.001**	14.5 (-19 to 48)	0.775

*, **: significant at p<0.05, p<0.001 respectively; **95% CI:** 95% Confidence Interval; \bar{d} : Mean difference (Newtons)

Although, the difference in treatment effect between groups was non-significant, the increase in strength in the Kneehab group from 6-12 weeks was significantly greater than the PRT group (Table 23). This is illustrated in Figure 19.

Table 23 Between Group Treatment Effects for Plantar-Flexor Strength (Newtons) – Impaired Side

Repeated Measures of ANOVA (p-value)	Post-Hoc Analysis (p-value)		
	0-6 Weeks	6-12 Weeks	0-12 Weeks
0.354	0.954	0.046*	0.354

* : significant at $p < 0.05$

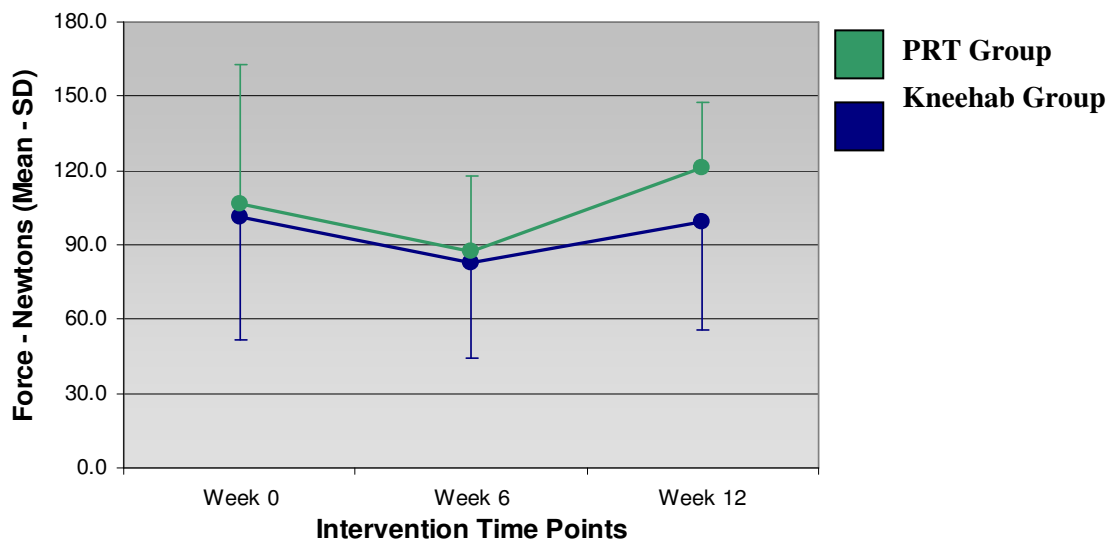


Figure 19 Group Treatment Effects - Plantar-Flexor Strength

Gluteus Maximus Strength – Impaired Side

The gluteus maximus strength of the Kneehab group was 12 N greater than the PRT group at baseline (Table 24). Both groups demonstrated high variability in their strength at all intervention time points. In the PRT group, strength increased throughout the intervention. The Kneehab group’s strength increased during the first weeks of the intervention and subsequently decreased during the second 6 weeks. The treatment effect was significant in both groups. Participants did not exceeded the 220 N measurement at any time point.

Table 24 Descriptive Statistics and Within Group Treatment Effect for Gluteus Maximus Strength (Newtons) – Impaired Side

Group	Mean (Standard Deviation)			Repeated Measures of ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	37.3 (± 15.1)	46.8 (± 18.9)	57 (± 27.5)	0.018*
Kneehab (n=15)	49.5 (± 30.8)	62.5 (± 35.9)	58.7 (± 31.3)	0.027*

Mean (SD): Newtons; *: significant at p<0.05

In the Kneehab group, the treatment effect was significant during the 0-6 week intervention period (**Table 25**). In addition, from 0-12 weeks the increase in strength in the Kneehab group approached significance, despite decreasing from 6-12 weeks. The change in the PRT group’s strength was non-significant throughout despite a 20 N increase from 0-12 weeks. There was high variability in the inter-individual change in strength in both groups (**Appendix 11**).

Table 25 Post-Hoc Analysis of Within Group Treatment Effect for Gluteal Strength (Newtons) – Impaired Side

Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	\bar{d} (95% CI)	p-value	\bar{d} (95% CI)	p-value	\bar{d} (95% CI)	p-value
PRT (n=10)	9.5 (-6.5 to 25.4)	0.350	10.2 (-3.9 to 24.4)	0.188	19.7 (-3.5 to 42.9)	0.103
Kneehab (n=15)	13 (0.4 to 25.6)	0.042*	-3.8 (-19.2 to 11.5)	1.00	9.2 (-0.2 to 18.6)	0.056

* : significant at p<0.05; **95% CI:** 95% Confidence Interval; \bar{d} : Mean Difference (Newtons)

There was no significant difference between groups in treatment effect during any intervention period (**Table 26**), despite a greater increase (10 N) in the PRT group from 0-12 weeks (**Figure 20**).

Table 26 Between Group Treatment Effect for Gluteal Strength (Newtons) – Impaired Side

Repeated Measures of ANOVA (p-value)	Post-Hoc Analysis (p-value)		
	0-6 Weeks	6-12 Weeks	0-12 Weeks
0.184	0.626	0.091	0.245

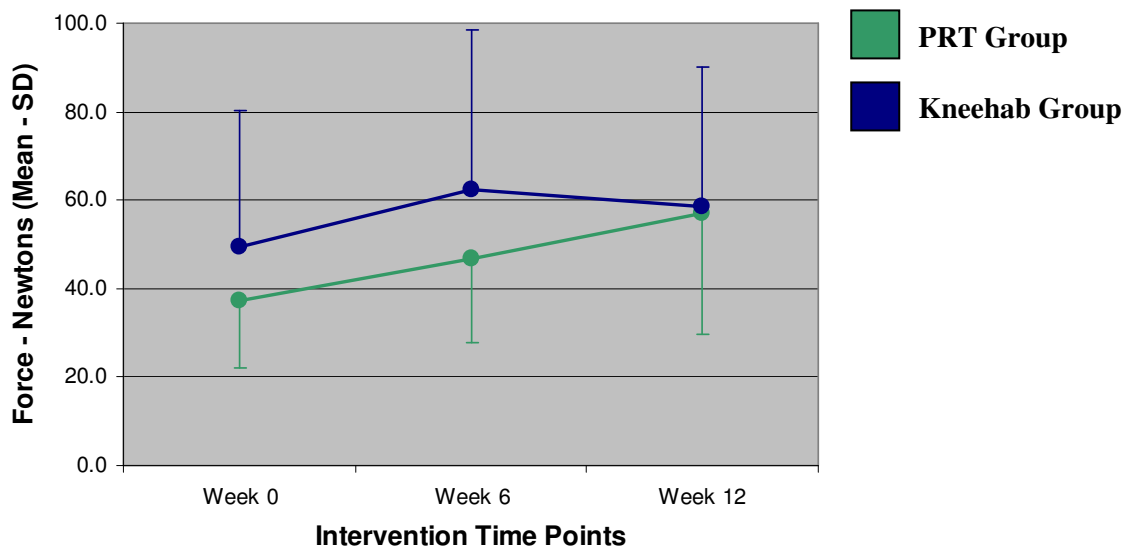


Figure 20 Group Treatment Effects - Gluteal Strength

Rectus Femoris Thickness – Impaired Side

The PRT group’s RF thickness was 0.2 centimetres (cm) greater than the Kneehab group at baseline (**Table 27**). In both groups, there was high variability in RF thickness throughout the intervention. There was no change in the PRT group’s muscle thickness from 0-12 weeks. In the Kneehab group, there was a significant increase (0.13 cm) in muscle thickness.

Table 27 Descriptive Statistics and Within Group Treatment Effect for Rectus Femoris Thickness (Centimetres) – Impaired Side

Group	Mean (Standard Deviation)			Repeated Measures ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	1.74 (± 0.42)	1.70 (± 0.38)	1.74 (± 0.41)	0.464
Kneehab (n=15)	1.54 (± 0.40)	1.53 (± 0.36)	1.67 (± 0.43)	0.045*

Mean (SD): Centimetres; * : significant at p<0.05

There were no significant within-group treatment effects for any intervention period in either group, with all 95% CIs passing through zero (**Table 28**). However, the increase in muscle thickness in the Kneehab group from 6-12 weeks approached significance. In both groups, the participants demonstrated high variability in their direction of change throughout the intervention (**Appendix 11**).

Table 28 Post-Hoc Analysis of Within Group Treatment Effect for Rectus Femoris Thickness (Centimetres) – Impaired Side

Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	\bar{d} (95% CI)	p-value	\bar{d} (95% CI)	p-value	\bar{d} (95% CI)	p-value
PRT (n=10)	-0.04 (-0.16 to 0.07)	0.855	0.04 (-0.07 to 0.16)	0.922	0 (-0.12 to 0.12)	1.00
Kneehab (n=15)	-0.01 (-0.17 to 0.16)	1.00	0.14 (-0.01 to 0.29)	0.055	0.13 (-0.05 to 0.32)	0.199

95% CI: 95% Confidence Interval; \bar{d} : Mean Difference(Centimetres)

There was no significant difference in treatment effects between groups (**Table 29**), despite the increase in the Kneehab group muscle thickness being 0.1 cm

greater than the PRT group, from 6-12 weeks. The differences in change are illustrated in **Figure 21**.

Table 29 Between Group Treatment Effects for Rectus Femoris Thickness (Centimetres) – Impaired Side

Repeated Measures of ANOVA (p-value)	Post-Hoc Analysis (p-value)		
	0-6 Weeks	6-12 Weeks	0-12 Weeks
0.140	0.604	0.147	0.140

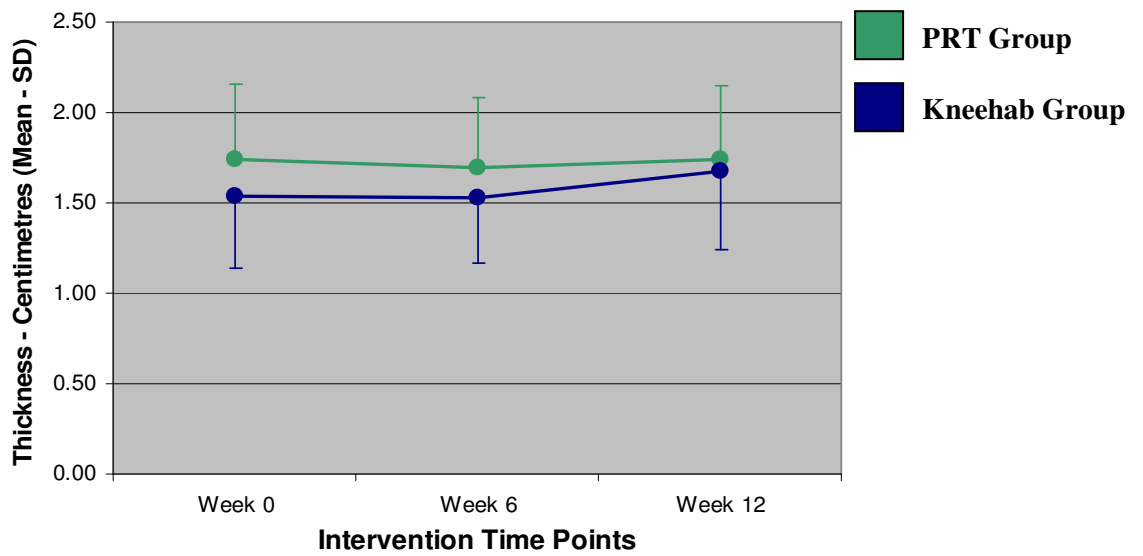


Figure 21 Group Treatment Effect – Rectus Femoris Thickness

Vastus Intermedius (VI) Thickness – Impaired Side

At baseline the VI thickness of the groups was similar (**Table 30**). The PRT group demonstrated higher variability than the Kneehab group throughout the intervention, with wide IQR relative to the median. Both groups' muscle thickness decreased from 0-6 weeks and increased from 6-12 weeks. There was no significant treatment effect in either group.

Table 30 Descriptive Statistics and Within Group Treatment Effect for Vastus Intermedius Thickness (Centimetres) – Impaired Side

Group	Median (Interquartile Range)			Friedman ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	1.28 (1.09)	1.20 (1.11)	1.36 (1.14)	0.617
Kneehab (n=15)	1.23 (0.49)	1.14 (0.58)	1.22 (0.61)	0.384

Median (IQR): Centimetres

In the PRT group, there were no significant treatment effects for any intervention period (**Table 31**). **Figure 22** demonstrates that the PRT group's muscle thickness did not change during the intervention. In the Kneehab group, although there was no significant treatment effect for the ANOVA, from 6-12 weeks there was a significant treatment effect. This appears to be due to the higher number of participants whose muscle thickness increased during this period (10), compared to the other intervention periods. Generally, there was inconsistent change in muscle thickness between participants in both groups (**Appendix 11**).

Table 31 Post-Hoc Analysis of Within Group Treatment Effect for Vastus Intermedius (Thickness) – Impaired Side

Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=10)	0 (0 : 3 : 7)	0.250	-0.01 (5 : 5 : 0)	0.625	-0.07 (4 : 6 : 0)	0.984
Kneehab (n=15)	0.01 (8 : 7 : 0)	0.552	0.05 (10 : 4 : 1)	0.040*	0.08 (9 : 6 : 0)	0.155

* : significant at $p < 0.05$; **Ranks:** Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (Centimetres).

There was no significant difference in the treatment effect between groups (Table 32). This is illustrated in Figure 22.

Table 32 Between Group Treatment Effect for Vastus Intermedius Thickness (Centimetres) – Impaired Side

Post-Hoc Analysis (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.354	0.693	0.539

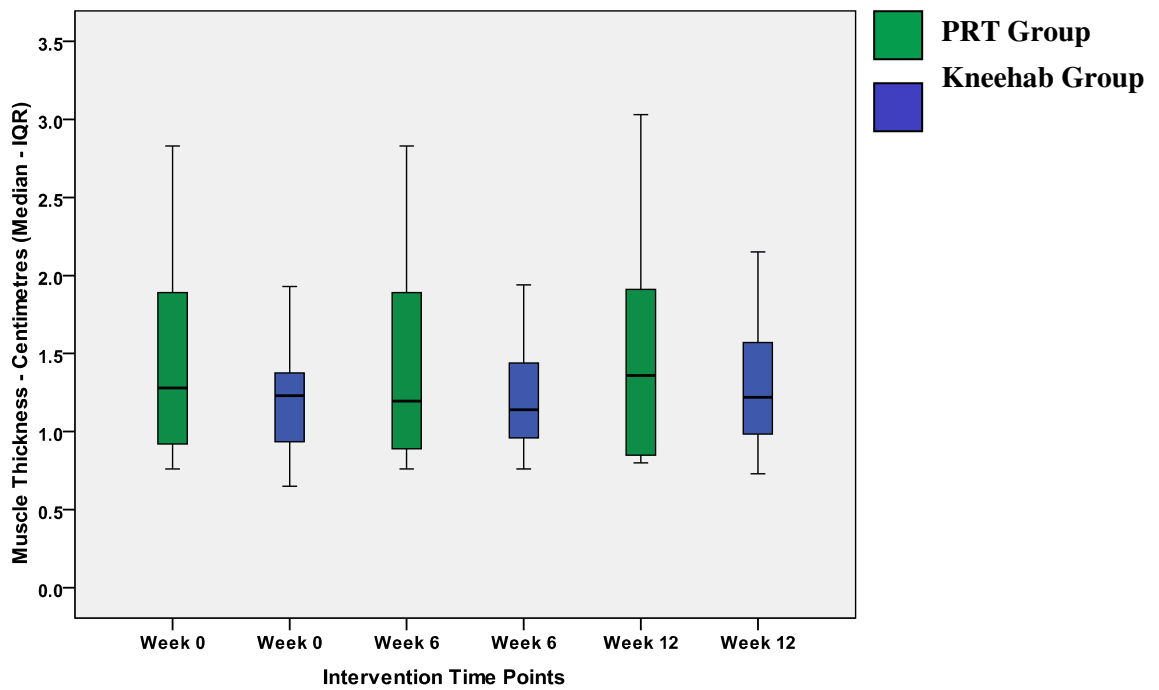


Figure 22 Group Treatment Effect – Vastus Intermedius Thickness

Quadriceps Endurance

The Kneehab group’s median endurance at baseline was 6 repetitions higher than the PRT group (**Table 33**). Both groups demonstrated high variability throughout the intervention, with a number of outliers (**Figure 23**). The Kneehab group’s endurance increased from week 0 to 12. In the PRT group, the change in endurance was not consistent throughout the intervention. In both groups, the within-group treatment effect was non-significant.

Table 33 Descriptive Statistics and Within Group Treatment Effect for Quadriceps Endurance (Repetitions) – Impaired Side

Group	Median (Interquartile Range)			Friedman ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	12 (33.3)	27 (31.3)	21.5 (40.8)	0.615
Kneehab (n=15)	18 (17)	21 (23)	33 (68)	0.116

Median (IQR): Repetitions

There was no significant within-group treatment effect in the PRT group, throughout the intervention (**Table 34**). The ranks demonstrate inconsistent change in PRT participants’ endurance from 0-12 and 6-12 weeks. In the Kneehab group there was a significant treatment effect from 0-12 weeks, with 9 participants’ endurance increasing and a median increase of 11 repetitions. From 0-6 weeks, the increase in 10 participants’ endurance approached significance.

Table 34 Post-Hoc Analysis of Within Group Treatment Effect for Quadriceps Endurance (Repetitions) – Impaired Side

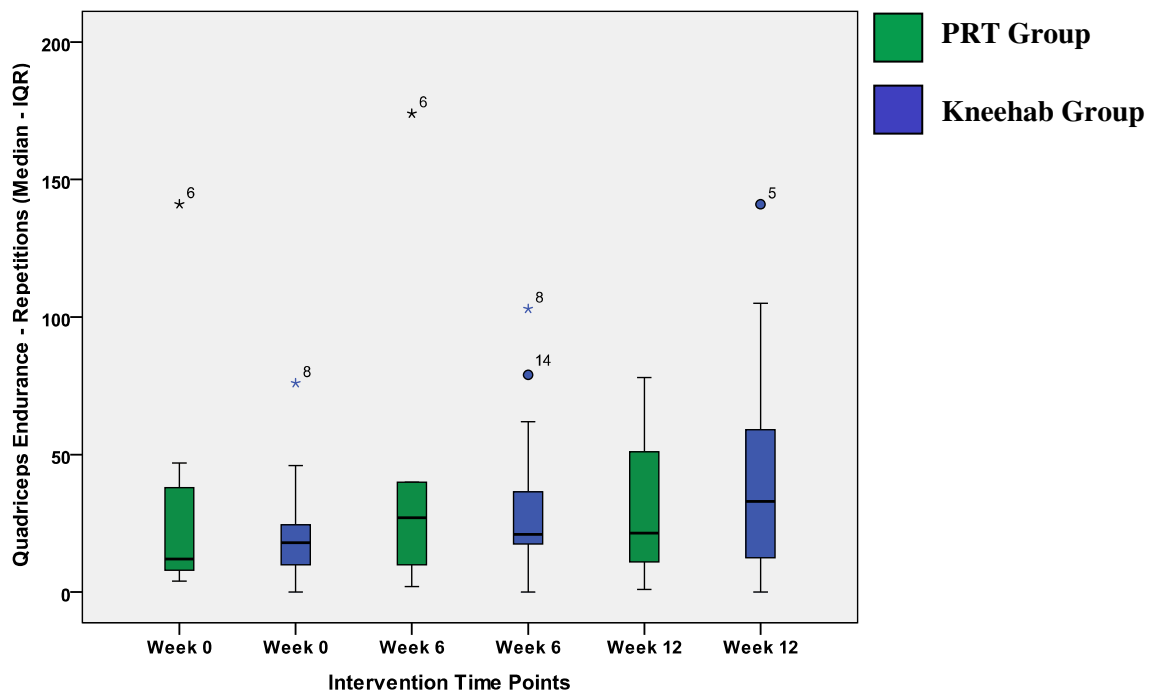
Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=10)	4.5 (7 : 3 : 0)	0.184	0.5 (5 : 5 : 0)	0.902	2.5 (5 : 4 : 1)	0.545
Kneehab (n=15)	5 (10 : 4 : 1)	0.065	2 (11 : 3 : 1)	0.123	11 (9 : 5 : 1)	0.043*

* : significant at $p < 0.05$; **Ranks:** Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (Repetitions).

There was no significant difference between groups for treatment effect during any intervention period (**Table 35**). This is illustrated by the similar increases in the groups' quadriceps endurance (**Figure 23**).

Table 35 Between Group Treatment Effect for Quadriceps Endurance (Repetitions) – Impaired Side

Post-Hoc Analysis (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.902	0.420	0.201



*6,8 or °5,14: denotes outliers

Figure 23 Group Treatment Effect – Quadriceps Endurance

Lower Limb Spasticity- Visual Analogue Scale

The number of participants in both groups reporting lower limb spasticity affecting their daily activities was small (**Table 36**). Although, the baseline median rating of spasticity was similar between groups, the Kneehab group demonstrated greater variability with a wide IQR. There was a significant treatment effect in the Kneehab group, with ratings of spasticity decreasing. In the PRT group, there was a 2 cm increase in spasticity rating from 0-12 weeks, and no significant treatment effect.

Table 36 Descriptive Statistics and Within Group Treatment Effect for Lower Limb Spasticity (Millimetres on VAS)

Group	Median (Interquartile Range)			Friedman ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=4)	35.2 (46.8)	54.6 (70.4)	37 (60.1)	0.361
Kneehab (n=6)	39.6 (80.8)	3.5 (32.4)	3.7 (5.7)	0.028*

Median (IQR): Millimetres; * : significant at $p < 0.05$

Although the ANOVA for the Kneehab group demonstrated a significant treatment effect, during the intervention periods there were no significant treatment effects (**Table 37**). From 0-6 and 0-12 weeks, however, the Kneehab group's improvements approached significance with the medians of the change scores decreasing. The small sample size and high variability may account for the lack of significance. In the PRT group there were no significant treatment effects during any intervention period.

Table 37 Post-Hoc Analysis of Within Group Treatment Effect for Lower Limb Spasticity (Millimetres on VAS)

Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=4)	13.4 (3 : 0 : 1)	0.250	-2.4 (1 : 3 : 0)	0.375	0.3 (2 : 2 : 0)	1.00
Kneehab (n=6)	-4.4 (1 : 5 : 0)	0.065	-16.3 (2 : 3 : 1)	0.870	-42.4 (0 : 6 : 0)	0.083

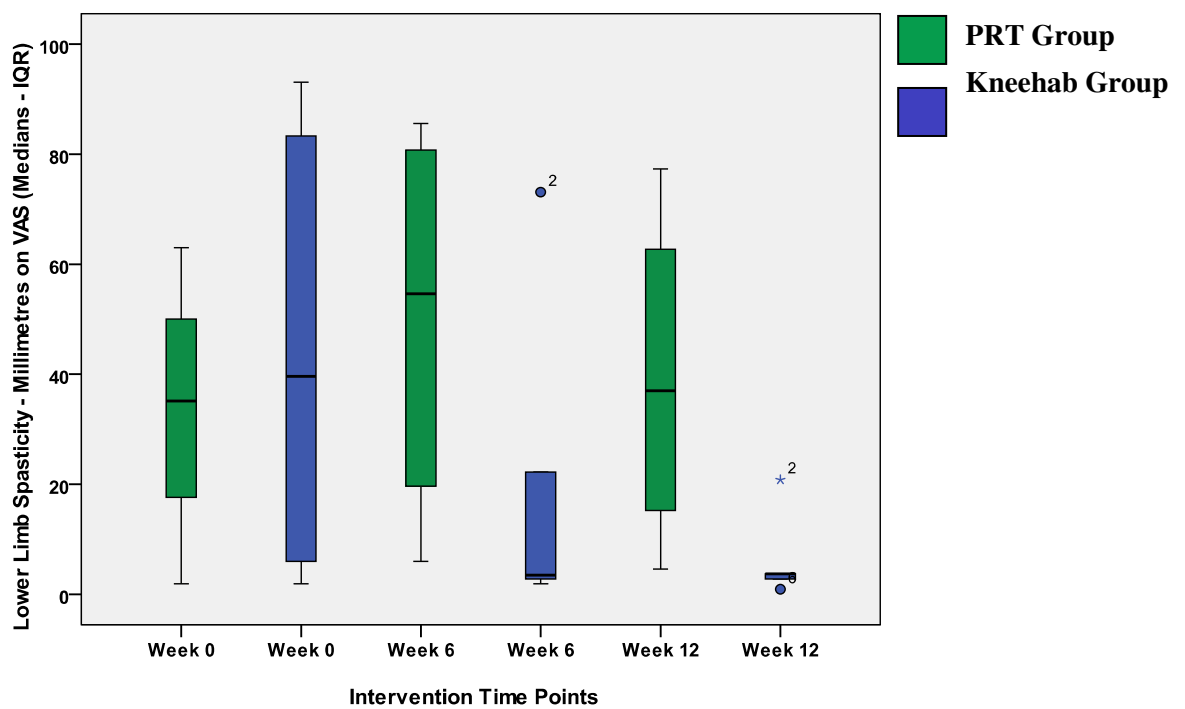
Ranks: Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (Millimetres).

There was a significant difference in the treatment effect between groups from 0-6 weeks (**Table 38**). The difference in the change in the Kneehab group's spasticity compared to the PRT group from 0-6 weeks is illustrated in **Figure 24**.

Table 38 Between Group Treatment Effect for Lower Limb Spasticity (Millimetres on VAS)

Post-Hoc Analysis (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.0.19*	1.00	0.171

* : significant at $p < 0.05$



*2 or °2,6: denotes outliers

Figure 24 Group Treatment Effect – Lower Limb Spasticity

5.4.5 Treatment Effect for Activity Outcomes

The data for all activity outcomes were non-normally distributed.

Balance – Berg Balance Scale

The groups demonstrated similar balance scores at baseline and variability throughout the intervention (**Table 39**). Balance improved in both groups during the intervention. The within-group treatment effect was significant in both groups.

Table 39 Descriptive Statistics and Within Group Treatment Effect for Balance (BBS Score)

Group	Median (Interquartile Range)			Friedman ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	38.5 (14.3)	46 (14.3)	46.5 (16.5)	0.032*
Kneehab (n=15)	40 (17)	42 (17)	46 (12)	<0.001**

Median (IQR): Berg Score; *, **: significant at $p < 0.05$, $p < 0.001$ respectively

The treatment effect in the PRT group approached significance from 0-6 and 0-12 weeks, with balance improving in 7 and 9 participants respectively (**Table 40**). In the Kneehab group, the treatment effect was significant during all intervention periods. The number of increasing ranks indicated that the majority of participants' balance improved during each intervention period.

Table 40 Post-Hoc Analysis of Within Group Treatment Effect for Balance (BBS Score)

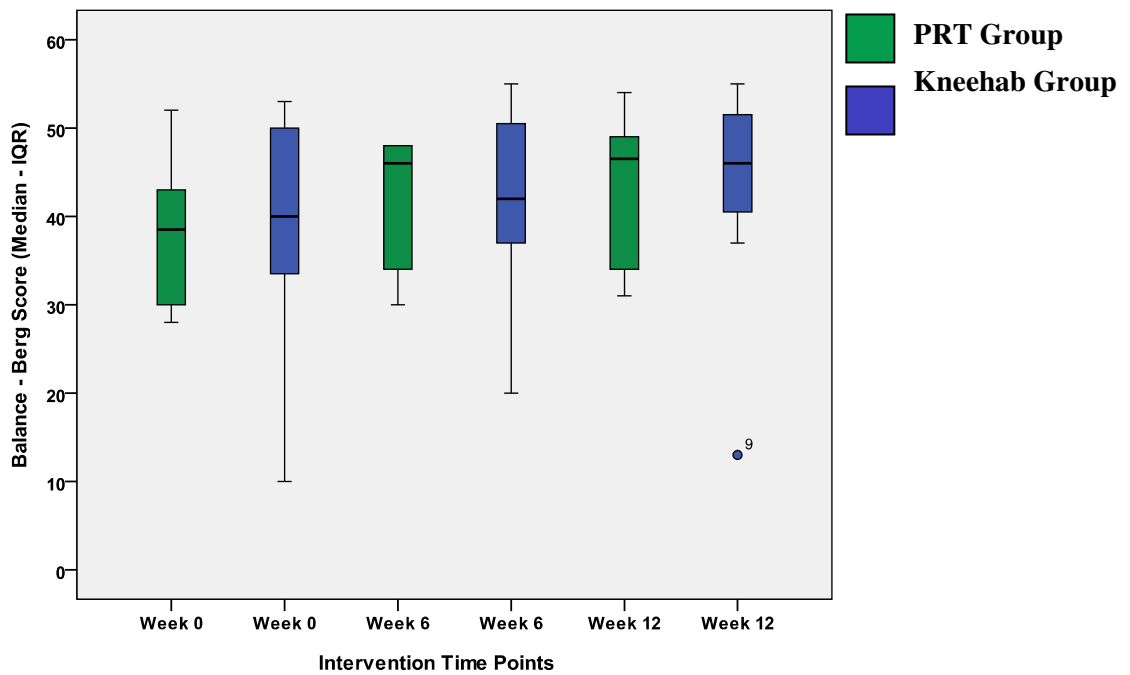
Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=10)	3.5 (7 : 3 : 0)	0.090	2 (6 : 3 : 1)	0.305	5 (9 : 1 : 0)	0.059
Kneehab (n=15)	2 (11 : 3 : 1)	0.004*	2 (10 : 1 : 4)	0.038*	4 (14 : 1 : 0)	<0.001**

*, **: significant at $p < 0.05$, $p < 0.001$ respectively; **Ranks:** Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (Millimetres).

There was no significant difference in treatment effect between the groups (Table 41). This is illustrated by the similar improvements in balance in both groups (Figure 25).

Table 41 Between Group Treatment Effect for Balance (BBS Score)

Post-Hoc Analysis (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.732	0.838	0.858



○9: denotes outlier

Figure 25 Group Treatment Effect – Balance

Mobility – Timed Up & Go Test

One participant in the Kneehab group could not perform this test on the final assessment day due to fatigue. The mobility time of the groups was similar at baseline (**Table 42**). The variability in mobility time was high in both groups. The medians demonstrate an improvement in mobility time in both groups. The within-group treatment effect approached significance in the Kneehab group.

Table 42 Descriptive Statistics and Within Group Treatment Effect for Mobility (TUG Seconds)

Group	Median (Interquartile Range)			Friedman ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	20.2 (11.2)	17.7 (23.2)	16.1 (25.4)	0.974
Kneehab (n=14)	21.2 (21.9)	18.1 (27.2)	17.2 (22)	0.080

Median (IQR): Seconds

In both groups, there were no significant treatment effects during any of the intervention periods (**Table 43**). There was no consistent change in mobility time, across participants, in both groups. In the Kneehab group there was a greater proportion of participants whose mobility time decreased from 0-6 and 0-12 weeks, compared to the PRT group. This indicates a trend for greater improvement in mobility in the Kneehab group.

Table 43 Post-Hoc Analysis of Within Group Treatment Effect for Mobility (TUG Seconds)

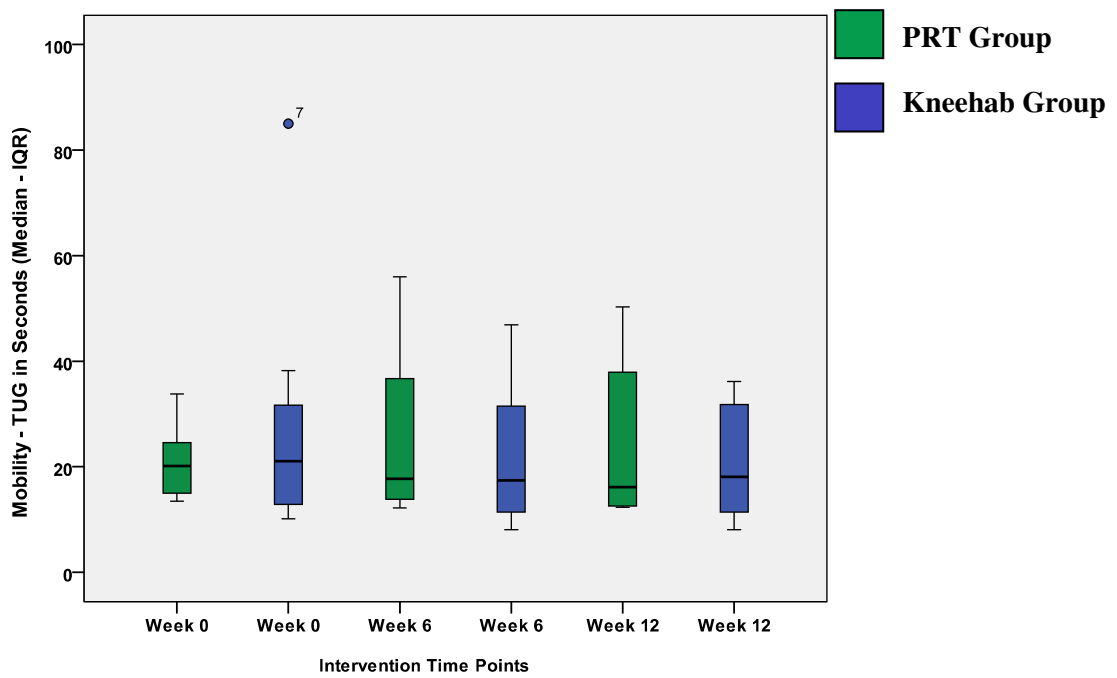
Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=10)	0.9 (6 : 4 : 0)	0.770	-0.1 (5 : 5 : 0)	0.678	-0.6 (4 : 6 : 0)	0.695
Kneehab (n=14)	-1.8 (4 : 10 : 0)	0.194	0.3 (7 : 7 : 0)	0.843	-1.4 (3 : 11 : 0)	0.135

Ranks: Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (Seconds).

There was no significant difference in the treatment effect between groups (Table 44). This is demonstrated in Figure 26, where the difference in change in mobility speed between groups is small.

Table 44 Between Group Treatment Effect for Mobility (TUG Seconds)

Post-Hoc Analysis (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.285	0.841	0.241



○7: denotes outlier

Figure 26 Group Treatment Effect – Mobility (TUG)

Mobility – Multiple Sclerosis Walking Scale-12

The groups were similar at baseline for self-reported mobility (**Table 45**). In the Kneehab group, variability was higher at all intervention points. Both groups' self-reported mobility improved during the intervention. The within-group treatment effect was close to significant in the PRT group.

Table 45 Descriptive Statistics and Within Group Treatment Effect for Mobility (MSWS-12)

Group	Median (Interquartile Range)			Friedman ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	49.9 (11.8)	41.5 (10.5)	38.5 (19.8)	0.067
Kneehab (n=15)	48 (17)	36 (25)	38 (26)	0.286

Median (IQR): MSWS-12 Score

There was no significant treatment effect during any intervention period for either group (**Table 46**). The change in mobility scores was inconsistent between participants in both groups throughout the intervention. This is demonstrated throughout the intervention by the similar proportions of increasing and decreasing ranks in the respective groups.

Table 46 Post-Hoc Analysis of Within Group Treatment Effect for Mobility (MSWS-12)

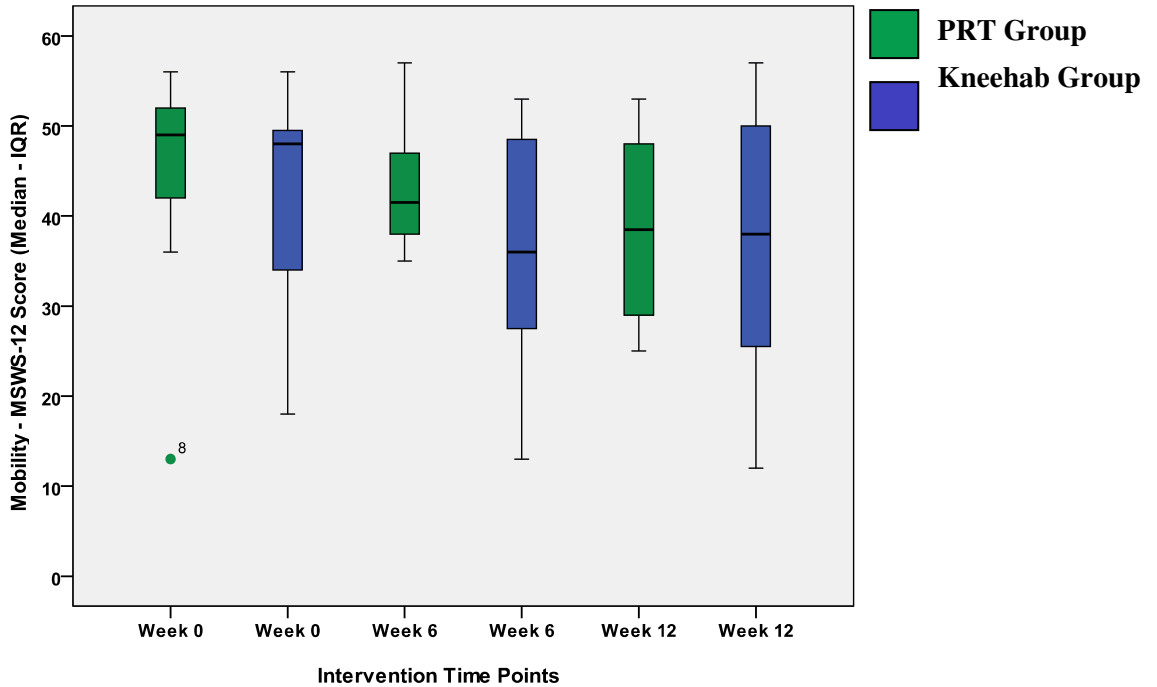
Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=10)	-2 (2 : 7 : 1)	0.164	-5 (3 : 6 : 1)	0.102	-5 (2 : 8 : 0)	0.137
Kneehab (n=15)	-7.5 (6 : 9 : 0)	0.132	1.5 (8 : 6 : 0)	0.572	-6.5 (4 : 11 : 0)	0.173

Ranks: Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (MSWS-12 Score).

There was no significant difference in treatment effects between groups for mobility (**Table 47**). This is illustrated by the similar change for both groups in **Figure 27**.

Table 47 Between Group Treatment Effects for Mobility (MSWS-12)

Post-Hoc Analysis (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.632	0.125	0.967



○8: denotes outliers

Figure 27 Group Treatment Effect – Mobility (MSWS-12)

5.4.6 Treatment Effect for Participation Outcomes

The data for the participation outcomes were non-normally distributed.

HRQoL – Multiple Sclerosis Impact Scale-29v2 (Total)

At baseline, the Kneehab group’s total HRQoL score was 8 points higher than the PRT group (**Table 48**); however, this difference was statistically non-significant. High variability in HRQoL score was evident in both groups at all intervention points. Throughout, both groups’ HRQoL improved. The within-group treatment effect was significant in the Kneehab group.

Table 48 Descriptive Statistics and Within Group Treatment Effect for Health Related Quality of Life (MSIS-29v2 Total Score)

Group	Median (Interquartile Range)			Friedman ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	33.3 (33.6)	28.2 (38.8)	27.6 (17.8)	0.353
Kneehab (n=15)	41.4 (39.1)	29.9 (27.6)	24.1 (37.9)	<0.001**

Median (IQR): MSIS-29v2 Total Score; **: significant at p<0.001

There was no significant treatment effect in the PRT group for any intervention period (**Table 49**). The PRT participants’ change in HRQoL varied for the intervention periods. In the Kneehab group, there was a significant treatment effect from 0-6 weeks, with 12 participants’ improving. This effect was maintained from the 6-12 week intervention period resulting in a significant treatment effect from 0-12 weeks, with 13 participants improving.

Table 49 Post-Hoc Analysis of Within Group Treatment Effect for Health Related Quality of Life (MSIS-29v2 Total Score)

Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=10)	3.4 (6 : 4 : 0)	0.510	-6.3 (6 : 4 : 0)	0.113	-2.9 (3 : 6 : 1)	0.563
Kneehab (n=15)	-8 (3 : 12 : 0)	0.004*	-1.1 (5 : 10 : 0)	0.412	-6.9 (0 : 13 : 2)	<0.001**

*, **: significant at p<0.05, p<0.001 respectively; **Ranks:** Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (MSIS-29v2 Total Score).

There was a significant difference in treatment effect between groups from 0-6 weeks (**Table 50**). This difference is illustrated in **Figure 28**, where the Kneehab group's HRQoL score decreased, while the PRT group's score increased.

Table 50 Between Group Treatment Effect for Health Related Quality of Life (MSIS-29v2 Total Score)

Post-Hoc Analysis (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.034*	0.331	0.147

* : significant at $p < 0.05$

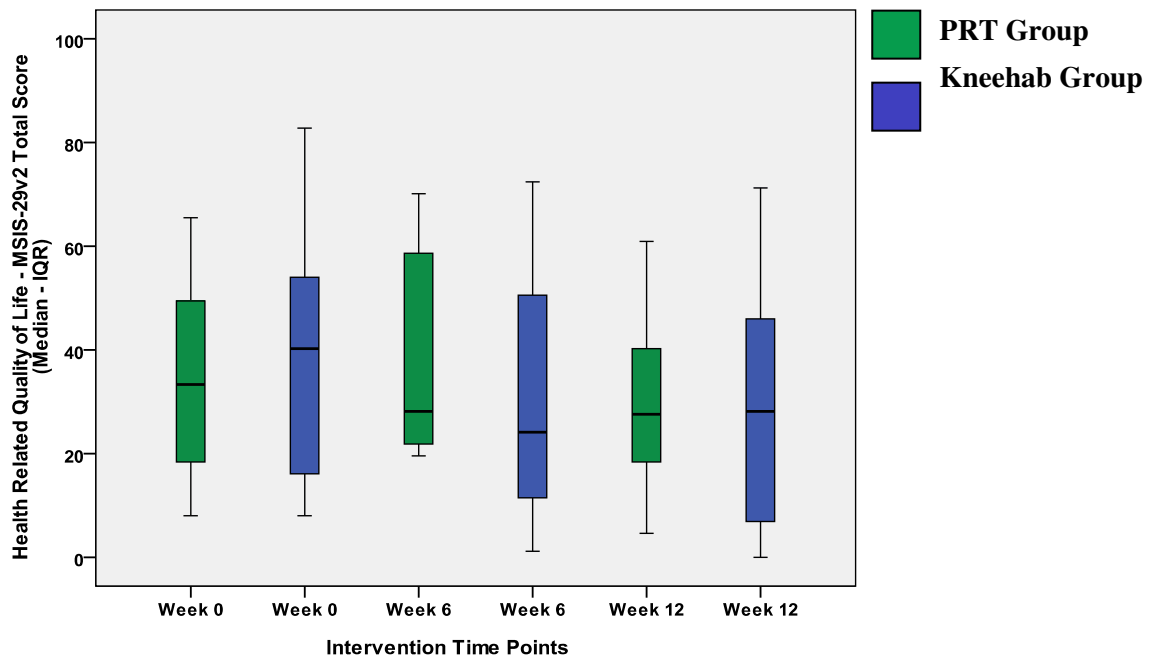


Figure 5.28 Group Treatment Effect – Health Related Quality of Life (MSIS-29v2 Total Score)

HRQoL – Multiple Sclerosis Impact Scale-29v2 (Physical Subscale)

Similar to the total score, the Kneehab group had a higher impact of MS (7.5 points) on their Physical HRQoL score at baseline (**Table 51**). Variability was high in both groups. There was an improvement in HRQoL on this subscale with decreasing medians in both groups. The within-group treatment effect was significant in the Kneehab group only.

Table 51 Descriptive Statistics and Within Group Treatment Effect for Health Related Quality of Life (MSIS-29v2 Physical Subscale Score)

Group	Median (Interquartile Range)			Friedman ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	42.5 (38.3)	35.8 (40.8)	34.2 (31.2)	0.353
Kneehab (n=15)	50 (43.3)	40 (40)	31.7 (36.7)	0.005*

Median (IQR): MSIS-29v2 Physical Subscale Score; * : significant at p<0.05

In the PRT group there was no significant within-group treatment effect during any of the intervention periods (**Table 52**). The variability in change in the group is evident from the ranks. The treatment effect was significant during the 0-6 week period in the Kneehab group, with 11 participants' score improving. The median decrease of 1.7 points from 6-12 weeks maintained the treatment effect, resulting in a significant effect from 0-12 weeks, with 13 participants improving.

Table 52 Post-Hoc Analysis of Within Group Treatment Effect for Health Related Quality of Life (MSIS-29v2 Physical Subscale Score)

Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=10)	-2.5 (5 : 4 : 1)	0.602	-7.5 (2 : 6 : 2)	0.102	-1.7 (3 : 6 : 1)	0.527
Kneehab (n=15)	-10 (4 : 11 : 0)	0.006*	-1.7 (6 : 9 : 0)	0.309	-8.3 (1 : 13 : 1)	0.001*

* : significant at p<0.05; **Ranks:** Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (MSIS-29v2 Physical Subscale Score).

The 0-6 week treatment effect was significantly different between groups (Table 53). In Figure 29, the difference in treatment effect for 0-6 weeks is demonstrated, with the score decreasing in the Kneehab group and increasing in the PRT group.

Table 53 Between Group Treatment Effects for Quality of Life (MSIS-29v2 Physical Subscale Score)

Post-Hoc Analysis (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.034*	0.420	0.139

* : significant at $p < 0.05$

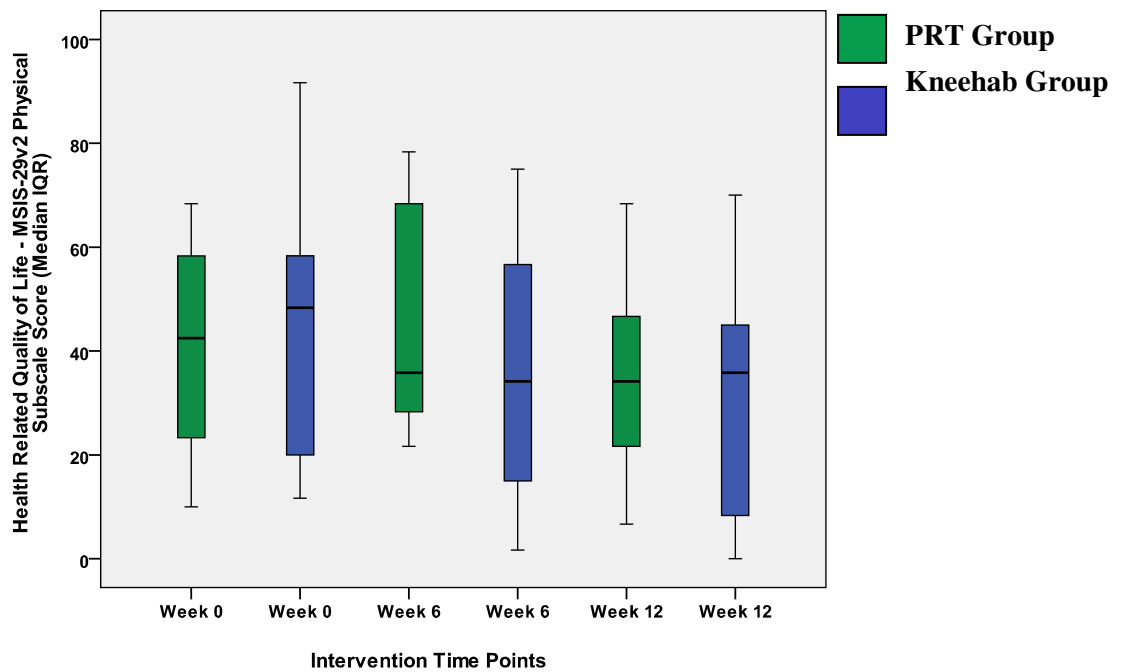


Figure 29 Group Treatment Effect – Health-Related Quality of Life (MSIS-29v2 Physical Subscale Score)

HRQoL – Multiple Sclerosis Impact Scale-29v2 (Psychological Subscale)

At baseline, the Kneehab group’s score on the psychological HRQoL subscale was 5.5 points higher than the PRT group (Table 54). In both groups, high variability was evident at all intervention points. HRQoL improved throughout in both groups, with decreasing medians. The within-group treatment effect was non-significant in both groups.

Table 54 Descriptive Statistics and Within Group Treatment Effect for Health Related Quality of Life (MSIS-29v2 Psychological Subscale Score)

Group	Median (Interquartile Range)			Friedman ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=10)	20.4 (25)	20.4 (33.3)	14.8 (30.6)	0.268
Kneehab (n=15)	25.9 (33.3)	11.1 (22.7)	7.4 (22.7)	0.121

Median (IQR): MSIS-29v2 Psychological Subscale Score;

There were no significant effects during the intervention periods for the PRT group (Table 55). Similar to the previous HRQoL scores, there was no consistency in the change between participants in the PRT group. In the Kneehab group, from 0-6 weeks there was a significant treatment effect, with 10 participants improving.

Table 55 Post-Hoc Analysis of Within Group Treatment Effect for Health Related Quality of Life (MSIS-29v2 Psychological Subscale Score)

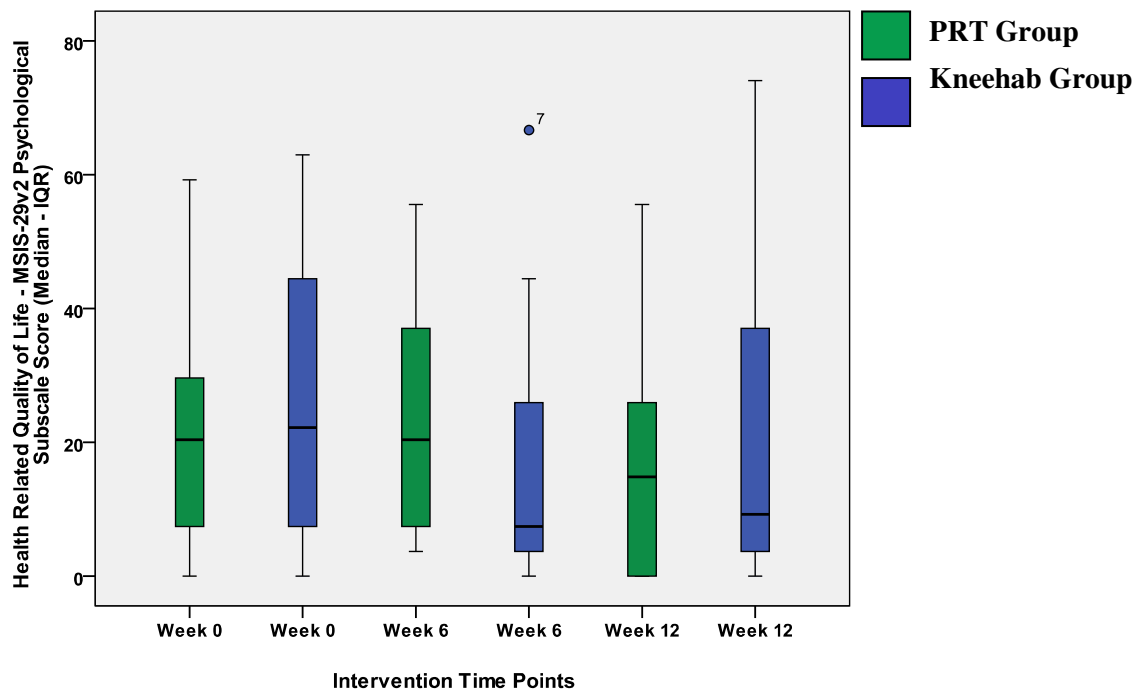
Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=10)	3.7 (5 : 3 : 2)	0.555	-3.7 (1 : 6 : 3)	0.125	0 (3 : 4 : 3)	0.688
Kneehab (n=15)	-3.7 (3 : 10 : 2)	0.019*	3.7 (8 : 4 : 3)	0.186	-3.7 (5 : 8 : 2)	0.114

* : significant at $p < 0.05$; **Ranks:** Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (MSIS-29v2 Psychological Subscale Score).

The difference in treatment effects between groups approached significance from 0-6 weeks and 6-12 weeks (Table 56). Figure 30 illustrates that the difference in effect from 0-6 weeks was due to HRQoL improving in the Kneehab group and worsening in the PRT group. From 6-12 weeks the difference in treatment effect was opposite.

Table 56 Between Group Treatment Effect for Quality of Life (MSIS-29v2 Psychological Subscale Score)

Post-Hoc Analysis (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.058	0.057	0.671



○7: denotes outliers

Figure 30 Group Treatment Effect – Health-Related Quality of Life (MSIS-29v2 Psychological Subscale Score)

Fatigue – Modified Fatigue Impact Scale

There was missing data for one participant in each group, for the fatigue score (Table 57). The fatigue in the Kneehab group was 5 points higher at baseline. The variability was high in both groups. There was a decrease in fatigue in both groups, throughout the intervention. There was a significant within-group treatment effect in the Kneehab group.

Table 57 Descriptive Statistics and Within Group Treatment Effect for Fatigue (MFIS Total Score)

Group	Median (Interquartile Range)			Friedman ANOVA (p-value)
	Week 0	Week 6	Week 12	
PRT (n=9)	40 (33.5)	38 (23.5)	39 (34)	0.971
Kneehab (n=14)	45 (22.3)	27.5 (31.8)	26 (31)	<0.001**

Median (IQR): MFIS Total Score; **: significant at p<0.001

There were no significant within-group treatment effects in the PRT group during any intervention period (Table 58). The participant change was inconsistent in the PRT group. There was a significant treatment effect from 0-6 weeks in the Kneehab group, with 13 participants' fatigue improving. This effect was maintained from 6-12 weeks, resulting in the significant treatment effect from 0-12 weeks, with all participants' fatigue improving.

Table 58 Post-Hoc Analysis of Within Group Treatment Effect for Fatigue (MFIS Score)

Group	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=9)	1 (5 : 4 : 0)	0.668	2 (6 : 3 : 0)	0.812	-2 (4 : 5 : 0)	0.645
Kneehab (n=14)	-19 (1 : 13 : 0)	<0.001**	0 (7 : 7 : 0)	0.469	-18 (0 : 14 : 0)	<0.001**

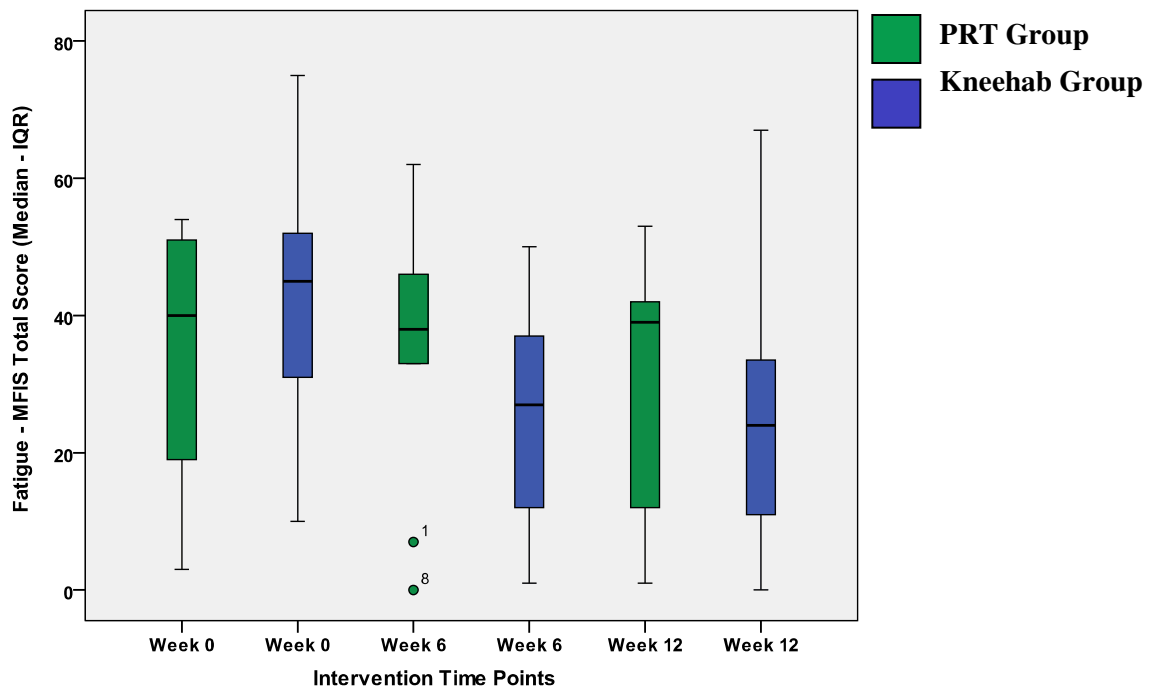
** : significant at p<0.001; **Ranks:** Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (MFIS Total Score).

The difference in treatment effects between groups was significant from 0-6 and 0-12 weeks (**Table 59**). These differences between groups in treatment effects are illustrated in **Figure 31**.

Table 59 Between Group Treatment Effect for Fatigue (MFIS Score)

Post-Hoc Analysis (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.008*	0.941	0.022*

* : significant at $p < 0.05$



○1,8: denotes outliers

Figure 31 Group Treatment Effect – Fatigue (MFIS Score)

5.4.7 Comparison of Volume of Exercise Completed

At the start of the intervention, there were no significant differences between the groups in the number of total and quadriceps repetitions ($p=0.705$; 0.491) completed, or the total or quadriceps work ($p=0.705$; 0.491) completed.

Repetitions

The mean number of total repetitions performed by participants in the Kneehab group was higher than participants in the PRT group throughout the intervention (**Table 60**). The difference between groups for total number of repetitions completed was non-significant.

Table 60 Descriptive Statistics and Between Group Differences for Total Repetitions

Time Interval	Mean (SD)		Independent T-Test
	PRT	Kneehab	p-value
0-6 weeks	1555 (\pm 473)	1857 (\pm 403)	0.111
6-12 weeks	2180 (\pm 718)	2591 (\pm 611)	0.130
0-12 weeks	3734 (\pm 900)	4407 (\pm 854)	0.298

Mean (SD): No. of Repetitions

There was a trend throughout the intervention for participants in the Kneehab group to complete more quadriceps repetitions than participants in the PRT (**Table 61**). The difference between the groups in the number of quadriceps repetitions completed approached significance from 0-6 weeks, favouring greater exercise volume in the Kneehab group.

Table 61 Descriptive Statistics and Between Group Differences for Quadriceps Repetitions

Time Interval	Mean (SD)		Independent T-Test
	PRT	Kneehab	p-value
0-6 weeks	991 (\pm 299)	1194 (\pm 274)	0.069
6-12 weeks	1428 (\pm 475)	1702 (\pm 435)	0.142
0-12 weeks	2419 (\pm 581)	2896 (\pm 589)	0.255

Mean (SD): No. of Repetitions

Work

The total work (repetition + weight) completed by participants in the Kneehab group was greater than participants in the PRT group throughout the intervention (**Table 62**). The difference in work completed between groups was significant from 6-12 weeks and close to significant 0-12 weeks.

Table 62 Descriptive Statistics and Between Group Differences for Total Work

Time Interval	Median (Inter-Quartile Range)		Mann-Whitney U Test
	PRT	Kneehab	p-value
0-6 weeks	1635 (985.3)	1987 (838.5)	0.186
6-12 weeks	2525 (3941)	6444 (6331.5)	0.049*
0-12 weeks	3822 (4503.3)	9600 (6955)	0.067

Median (IQR): Work (1 unit = 1 Repetition + 0 Kg; 2 units = 1 Repetition + 1 Kg); * : significant at $p < 0.05$

Participants in the Kneehab group completed more quadriceps work throughout the intervention than PRT group participants (**Table 63**). The amount completed by the Kneehab group participants was significantly greater 6-12 and 0-12 weeks.

Table 63 Descriptive Statistics and Between Group Differences for Quadriceps Work

Time Interval	Median (Inter-Quartile Range)		Mann-Whitney U Test
	PRT	Kneehab	p-value
0-6 weeks	992.5 (573.8)	1315 (652.5)	0.148
6-12 weeks	1519 (2175.5)	4384 (3544)	0.026*
0-12 weeks	2421 (2468)	6370 (3948.5)	0.036*

Median (IQR): Work (1 unit = 1 Repetition + 0 Kg; 2 units = 1 Repetition + 1 Kg); * : significant at $p < 0.05$

Sessions

The number of exercise sessions completed by the groups was the same 0-6 weeks (**Table 64**). However, participants in the Kneehab group completed more sessions 6-12 and 0-12 weeks. The difference between the groups was significant from 0-12 weeks.

Table 64 Descriptive Statistics and Between Group Differences for Number of Sessions

Time Interval	Median (Inter-Quartile Range)		Mann-Whitney U Test
	PRT	Kneehab	p-value
0-6 weeks	12 (2)	12 (1)	0.197
6-12 weeks	13 (6)	17 (4)	0.082
0-12 weeks	24 (4)	28 (5)	0.036*

Median (IQR): No. of Sessions; * : significant at $p < 0.05$

5.5 Discussion

5.5.1 Attrition and Baseline Differences

There was a higher attrition rate in the PRT group, which was due to benign reasons associated with MS, and poor compliance with the programme. In the Kneehab group, however, two participants experienced an adverse reaction to the stimulation, where muscle spasm was induced. On subsequent examination of the initial interview notes, it was found that both participants reported frequent spasticity, which occurred with small changes in stimulus. This suggests hypersensitivity as the cause of spasticity in these participants. The association between spasticity and hypersensitivity of the central nervous system (Ivanhoe and Reistetter 2004), suggests that these participants may have experienced muscle spasm due to the noxious nature of the NMES stimulus. Therefore, NMES may not be a suitable treatment option for PwMS whose spasticity is due to hypersensitivity to stimulus. All other participants tolerated the superimposition of NMES on functional PRT exercises, while PRT-only participants did not express any difficulties with the exercises. This indicates that home-based PRT with or without NMES is both feasible and safe.

At baseline, the demographic characteristics differed between the groups, such that there were more men and more people with a progressive type of MS in the PRT group. This suggests that the participants in the PRT group were more disabled as, men with MS have been shown to have lower HRQoL and are predisposed to an unfavourable prognosis (Casetta et al. 2009, Zaffaroni and

Ghezzi 2000), while progressive types of MS are associated with greater disability and poorer prognosis than a relapsing remitting type of MS (Thompson et al. 1997, Confavreux et al. 2000). The trend of higher isometric strength and quadriceps endurance at baseline in the Kneehab group supports the contention of a higher level of disability in the PRT group. However, Kneehab participants demonstrated a trend for worse HRQoL and fatigue. None of these differences were significant; therefore we cannot be certain that there was greater disability in either group. Objective measurement with the EDSS would have been ideal to determine differences in disability between the groups; however this was beyond the resource capability of the study.

5.5.2 Summary of Treatment Effects

In both groups, moderate to high variability on all outcomes at all evaluation points was demonstrated. This suggests heterogeneity in the level of disability within the groups. The within-group treatment effects were non-significant for quadriceps strength in the groups. However, there was a significant treatment effect for gluteal strength in both groups. There were also significant treatment effects for plantar-flexion strength, RF thickness, quadriceps endurance and spasticity in the Kneehab group. The intervention periods in which these effects occurred varied. Balance improved significantly in both groups, and in the Kneehab group during all 3 intervention periods. Although there was no statistically significant treatment effect for mobility in either group, there was a trend of improvement on both mobility measures in both groups, which may be of clinical value. For all HRQoL scores and fatigue, there were statistically significant treatment effects in the Kneehab group. These improvements were significant during the 0-6 week intervention period.

There were significant differences in treatment effects between the groups for plantar-flexion strength, spasticity, HRQoL (total score and physical subscale) and fatigue. All of these differences favoured greater improvement in the Kneehab group at varying intervention periods. In addition, intervention participation was significantly greater for the number of sessions completed (0-12 weeks), total work (6-12 weeks) and quadriceps work (0-12 and 6-12 weeks)

in the Kneehab group. There was also a trend for the Kneehab group to complete a greater number of repetitions.

5.5.3 Within-Group Treatment Effects

Isometric Strength

The non-significant increase in the primary outcome measure of isometric quadriceps strength in both groups was unexpected, as the intervention was aimed at improving this outcome. The post-hoc test for powering of the study, confirmed that the sample size was too small to detect a significant within-group effect for this outcome, in either group. A lack of significant effects may also be due to the high level of variability in the groups, indicated by the large standard deviations, for strength scores, at all evaluation points. The influence of a ceiling-effect from the HHD on the non-significant strength changes appears limited as only 1 participants exceeded the maximum measurement level of 220 N.

The change in quadriceps strength was not consistent between participants throughout, with some participant's strength increasing and others decreasing (**Appendix 11, Figure 38 & 41**). This was also an unexpected finding, which may have contributed to the non-significant effects for quadriceps strength. The inconsistent change in quadriceps strength may be due to a worsening of condition which is likely in progressive types of MS, diurnal variation in symptoms such as increased fatigue, differences in volume or intensity of exercise completed or DOMS, as participants exercised 2-3 days prior to the 6 and 12 week evaluations. In the Kneehab group, the quadriceps force achieved while wearing the device may also have been insufficient to achieve strength gains, possibly due to discomfort with the stimulation. However, whether the force output of superimposing NMES on voluntary contraction is greater than voluntary contraction alone needs to be confirmed in future studies.

Interestingly, the increase in strength that occurred in the Kneehab group, although small, occurred during the first 6 weeks of the intervention. A similar result was found in the study by Broekmans et al. (2011), where there was a

plateau in strength gains after the first 10 weeks of intervention, using both PRT and PRT with NMES. The PRT group in our study demonstrated similar increase in quadriceps strength from 0-6 and 6-12 weeks. The implications of these results are that the strength increases with PRT are gradual, whereas the addition of an NMES device may increase strengthening initially due to a neural training effect. This view is supported by the absence of a hypertrophy effect for the RF and VI in the first 6 weeks of intervention.

Previous PRT studies in the MS population have demonstrated significant quadriceps strength increases (DeBolt and McCubbin 2004, de Souza-Teixeira et al. 2009, Dalgas et al. 2009). Direct comparison of these strength changes to our study is limited by the differences in measurement technique and unit of measurement. Nonetheless, a change of 10 N in force in the PRT and Kneehab groups is a smaller treatment effect than the respective 20 and 38 Nm increases in force, in the Dalgas et al. (2009) and de Souza-Teixiera et al. (2009) studies. This indicates that there was no additional strengthening benefit of adding NMES to PRT. However, the lack of a treatment effect in our study, compared to these previous studies, may have been due to a number of issues.

First, the cohort in our study is likely to have been more disabled than participants in the Dalgas et al. (2009) and de Souza-Teixiera et al. (2009) studies, due to their use of a walking aid. This may have contributed to the variable strength changes seen, due to the association between more progressed disability and decreased clinical stability in condition (Confavreux et al. 2000). As a result, the magnitude of the treatment effect may have been reduced. Second, the training intensity that participants exercised at may have been lower than intended as progressions were indirectly supervised, via telephone calls. Accordingly, participants may not have been exercising to fatigue, and therefore were achieving a lower percentage of 1 repetition max compared to Dalgas et al. (2009), DeBolt and McCubbin (2004) and de Souza-Teixiera et al. (2009). Therefore, performing 4 quadriceps exercises at a low intensity with a maximum volume of 3 sets of 12 repetitions, may have resulted in an endurance training effect, rather than strengthening. This is supported by the significant improvements in quadriceps endurance seen in the Kneehab group, who

completed more repetitions. Finally, the measurement technique may also have been an issue, as there are a number of weaknesses associated with measuring strength with HHD (Kolber and Cleland 2005), that IKD testing overcomes. One of the primary issues was that participants performed isotonic muscle contractions, yet their strength was tested isometrically. Considering the specificity principle of resistance training (Ratamess et al. 2009), an IKD would have been more sensitive to change than an isometric test with a HHD.

The change in isometric gluteal strength was significant in both groups during the intervention, and for the Kneehab group from 0-6 weeks. This is a novel finding, as gluteal strength has not previously been evaluated in exercise intervention studies for PwMS. In both groups plantar-flexion strength improvements were significant. For the Kneehab group this treatment effect was significant during the 6-12 weeks intervention period. The improvements in both groups may have been exaggerated by a possible measurement error at mid-intervention which indicated a decrease in strength in all participants from 0-6 weeks. The effect of this may have been a misrepresentation of the change from 6-12 weeks.

The clinical relevance of these significant strength increases in both groups is unclear, as associations between isometric strength and functional activities were not demonstrated in **Chapter 4**. Nonetheless, there were concurrent significant improvements in balance in both groups, in physical HRQoL in the Kneehab group, and a trend for improvement in mobility in both groups. This suggests that the strength increases in both groups had a clinically relevant impact, considering the link between strength and function in the MS and other populations (Mevellec et al. 2003, Thoumie et al. 2005, Weiss et al. 2000, Kobayashi et al. 2011).

Quadriceps Thickness

In two recent studies (de Souza-Teixeira et al. 2009, Dalgas et al. 2010b), significant increases in quadriceps size post-PRT have been shown. The results of these studies are not directly comparable to our study, due to the use of MRI and muscle biopsy respectively. Nonetheless, the lack of a treatment effect in

the PRT group in our study suggests that the training intensity may not have been sufficient to induce hypertrophy. However, the statistically significant increase in RF thickness from weeks 6-12 in the Kneehab group is a novel finding, which suggests that adding NMES to PRT may result in a hypertrophy effect. The change in muscle thickness from 6-12 weeks is in line with the reported time frame for muscle size changes during PRT (Abe et al. 2000). Furthermore, identifying the time frame in which hypertrophy occurs in populations with neuromuscular disease, has been recommended (Kilmer 2002). Therefore, our result builds on the findings of Dalgas et al. (2010b) and de Souza-Teixeira et al. (2009).

An additional interesting finding was that hypertrophy only occurred in the RF of the Kneehab group. This may indicate that the NMES stimulation provided a hypertrophy effect due to the superficial position of the RF. A similar finding in a spinal cord injured population was made previously (Scremin et al. 1999). The deeper VI muscle may have received less stimulation as the Kneehab device uses a square wave-form, which has a reduced penetration depth compared to a sine wave-form (Petrofsky et al. 2008). The clinical implication is that regular NMES use with PRT may result in hypertrophy of the musculature that is closest to the stimulation, i.e. superficial.

The clinical value of this treatment effect must be considered in the context of the measurement method. First, as the measurement protocol was novel and the assessor was relatively inexperienced, measurement error was a possibility. This was demonstrated in the pilot of the protocol. As a result a high level of variability in muscle size change was seen, which limits the validity and subsequently clinical applicability of the significant treatment effect in the Kneehab group. Furthermore, a number of confounding variables have been identified with RTUS measurement of muscle size (Perkin et al. 2003). The second major issue relates to the limited amount of the quadriceps that was actually measured, with measurement of the RF and VI at one point only. Therefore, changes may or may not have occurred in other parts of these muscles, or the vastus medialis or vastus lateralis. Consequently, determining

whether the muscle thickness changes in the Kneehab group were of clinical value is restricted.

Quadriceps Endurance

Quadriceps endurance, measured with a repeated sit-to-stand test to fatigue, increased in both groups. However, the increase was only significant in the Kneehab group from 0-12 weeks of intervention. The novel nature of the measurement method limits direct comparison to other studies. Nonetheless, de Souza-Teixeira et al. (2009) and Taylor et al. (2004) measured muscle endurance respectively using repeated knee extension and leg press, to fatigue, which is similar to the measurement method in the present study. The Kneehab group's endurance increased by 45.5% compared to 84.1% and 170% in the de Souza-Teixeira et al. (2009) and Taylor et al. (2006) studies respectively. This indicates a smaller training effect in our protocol.

The treatment effect for quadriceps endurance in the PRT group was non-significant. This lack of a treatment effect compared to the Kneehab group may be partly explained by the fact that the Kneehab group performed a higher number of repetitions than the PRT group. In addition, the trend for higher strength in the Kneehab group may have contributed to their superior outcome, as lower limb muscle strength is a predictor of sit-to-stand performance (Lord et al. 2002).

From a clinical perspective, the significant increases in quadriceps endurance in the Kneehab group are important, as there were concurrent improvements in balance and mobility. In **Chapter 4**, the moderate associations between quadriceps endurance and balance, and quadriceps endurance and mobility, support the transfer of increases in muscular endurance to functional improvements. Therefore, the significant improvements in quadriceps endurance in the Kneehab group appear to be of clinical relevance.

Spasticity

The perceived impact of lower limb spasticity on daily activities was evaluated in this study. Statistically significant treatments effects were seen for this

measure in the Kneehab group only, from 0-6 weeks of intervention. In two previous studies, significant improvements for spasticity on the MAS were found in the short-term for PwMS, following electrical stimulation (Armutlu et al. 2003, Szecsi et al. 2009). Thus, our results substantiate the view that initial NMES use improves spasticity, subjectively as well as objectively.

The mechanism for the spasticity reduction in our study can only be speculated upon, as no physiological measures were taken. An inhibitory effect on the CNS may explain the reduced spasticity in the Kneehab group. This has been demonstrated previously in people who experience spasticity, via a reduction in the H-reflex or myoelectrical activity of the muscle, following electrical stimulation (Bakhtiary and Fatemy 2008, Armutlu et al. 2003).

The change in the median score from pre to post intervention for perceived spasticity in the Kneehab group was 90%. A change that exceeds 30% on a numerical rating scale for spasticity in PwMS, has been found to be a clinically important difference (CID) (Farrar et al. 2008). This suggests that the change in the Kneehab group may have been of clinical importance. However, this conclusion is limited by the different properties of a VAS and NRS. In addition, the generalisability of this result is low, due to the small number of people in the Kneehab group with spasticity (n=6). Thus, in order to confirm this result, future studies should aim to investigate the effects of NMES on spasticity in larger cohorts.

Balance

There were significant treatment effects for balance in both groups during the intervention. In the Kneehab group, the treatment effects were significant during all intervention periods. Although this suggests that 6 weeks of NMES is sufficient, the median change score from 0-6 weeks was 2, which is below the recommended minimal detectable change (MDC) values of 2.33 in PwMS (Paltamaa et al. 2008). After 12 weeks, the Kneehab group's median change score was 4, which gives us more certainty that actual change was detected. The PRT group exceeded the MDC after 6 and 12 weeks of intervention; however, these results were non-significant. Therefore, it is unclear whether 6 or 12 weeks

of PRT is sufficient to achieve change that is of clinical value. We can be more certain that 12 weeks of PRT with NMES does provide clinically relevant improvements in balance, as significant change above the MDC was achieved.

The positive effect of resistance training on balance in PwMS has been shown previously, using measures other than the BBS (DeBolt and McCubbin 2004, Ayán et al. 2007). Therefore, as highlighted earlier, strength and endurance increases may have contributed to the improvements in balance. In a study where dynamic standing exercises were performed (Cattaneo et al. 2007), the mean change of 4.6 on the BBS was similar to the median change in both groups in our study. A rehabilitation program based upon repeated weight bearing exercises is likely to induce neuroplastic changes according to motor learning theory (Ploughman 2002). Therefore, repeated task practice and functional movement may have contributed to the improvements in balance. Furthermore, both groups changed from a moderate risk of falls to a low risk of falls, with their post-intervention scores exceeding the recommended cut-off score of 45, for low risk of falls (Riddle and Stratford 1999). This change supports the clinical value of the improvements in balance in both groups. It remains to be seen whether the additional cost of adding an NMES device to PRT translates to a clinically significant improvement greater than PRT only.

Mobility

There were no statistically significant treatment effects on either mobility measure in the groups. On the TUG measure, the percentage change of the medians in the PRT (19.9%) and the Kneehab (18.8%) groups was similar to that in de Souza-Teixeira et al. (2009) (16.7%) and greater than the 9.3% improvement in Sabapathy et al. (2011), both of which were significant. The inter-individual variability in change in the groups in our study may account for the lack of statistical significance. To this author's knowledge, there are no comparable data for a physical intervention using the MSWS-12. However, in a study evaluating the drug fampridine, the MSWS-12 score decreased by 6.8 points, which was significant (Goodman et al. 2009). This change in the Goodman et al. (2009) study is similar to the non-significant median change of 6.5 points in the Kneehab group. The variability in change again appears to

explain the lack of significance. Consequently, interpreting the clinical value of these changes is limited by the inconsistent nature of the change between participants in the respective groups.

Health Related Quality of Life

In the Kneehab group, treatment effects were significant from 0-6 weeks for all HRQoL scores, and from 0-12 weeks for the total and physical subscale scores. There were no significant changes in the PRT group. A possible explanation for the significant treatment effects being seen in the Kneehab group and not the PRT group is that the Kneehab group had a higher HRQoL score at baseline. Consequently, Kneehab participants had greater potential for improvement.

In the PRT studies by Taylor et al. (2006) and Sabapathy et al. (2011), HRQoL was also evaluated on the MSIS-29. Changes of 33.3% and 10.3% in the respective studies on the physical subscale were shown to be significant. The percentage change in the Kneehab group (36.6%) was of greater magnitude. The significant improvement on the psychological subscale in the Kneehab group (71.4%) indicates a superior intervention effect compared to that of Taylor et al. (2009) (7.1%) and Sabapathy et al. (2011) (14.5%). The concurrent improvements in balance, mobility, strength, endurance, spasticity and fatigue in the Kneehab group may account for the better treatment effects than PRT alone. The significant improvements on the physical subscale can be explained by the fact that the intervention was aimed at improving physical condition. The reasons for the significant improvement on the psychological subscale in the Kneehab group only, are less clear. The number of contacts with the assessor did not differ between the groups; therefore the potential effect of discussing their condition and progress on a weekly basis as the mediator for this improvement can be discounted. A plausible explanation for the improvement in the Kneehab group is that psychological well-being is associated with exercise (Scully et al. 1998). Thus, the higher volume of exercise completed by the Kneehab group compared to the PRT group may explain the differences in treatment effects between the groups. These results imply that 6 weeks of NMES use is sufficient to achieve significant treatment effects, as there was no significant change from 6-12 weeks of intervention. Although it is tempting to conclude that 6 weeks of

NMES is sufficient, the effects may not have been maintained if device use was discontinued. Therefore, future studies should aim to elucidate whether continued NMES use is required to maintain improvements.

The significance of these treatment effects in a clinical context is difficult to determine, as the clinically important difference for the MSIS-29v2 has not been calculated. However, considering the median change of 10 points on the physical subscale, which has a range of 100, it appears reasonable to conclude that a clinically important change occurred. This is supported by the fact that there were significant improvements in balance and the impairments outcomes of strength, endurance and spasticity in the Kneehab group.

Fatigue

The significant treatment effects occurred in the Kneehab group only, from 0-6 and 0-12 weeks of intervention. Similar to the treatment effects for the HRQoL measure, the significant 0-12 week effects were due to the maintenance of the 0-6 week change during the 6-12 week period. The percentage change in the medians from 0-6 weeks was 38.8% compared to 24% in an 8 week PRT programme for PwMS who were less disabled than the present cohort (White et al. 2004). Therefore, the addition of the Kneehab device to a PRT programme appears to produce a better treatment effect on fatigue in a shorter period than PRT alone. The significant improvements in fatigue in the Kneehab group only, may be explained by the association between increased exercise and lower levels of fatigue, in MS and other populations that experience high levels of fatigue (Mostert and Kesselring 2002, Edmonds et al. 2004). However, since the difference in exercise volume between the groups was not significant for all of the variables tested, other factors may have influenced the improvements in fatigue in the Kneehab group, that were not seen in the PRT group. One possible explanation is that the Kneehab group experienced a placebo effect of having a device. The existence of such an effect needs to be confirmed in future studies.

Clinically, the improvements in fatigue in the Kneehab group were significant, considering the magnitude of change and the prevalence and severity of fatigue in PwMS.

5.5.4 Difference in Treatment Effects Between-Groups

There were significant differences in treatment effects between the groups for plantar-flexion strength, spasticity, HRQoL on the total and physical HRQoL scores, and fatigue. All significant differences favoured greater improvement in the Kneehab group, indicating a therapeutic benefit of adding the Kneehab device to a PRT programme. Although differences in disability level may account for the greater improvements in the Kneehab group, this cannot be confirmed as an objective measure of disability was not performed. Nonetheless, the trend of higher muscle strength and endurance compared to the PRT group at baseline may have been an influence on the volume of exercise the respective groups completed, and consequently the differences in outcomes. This is supported by the fact that a higher strength at baseline influences the intensity of training that can be completed in healthy older adults (Yamauchi et al. 2009). Another possible explanation is that the device provided a placebo effect that resulted in Kneehab participants perceiving a greater improvement than PRT participants, as the HRQoL, fatigue and spasticity measures were all subjective. A placebo effect whereby participants were motivated to do more exercise due to having the device may also have influenced the outcomes.

The difference in treatment effect for plantar-flexion strength may have resulted from an exaggeration in effect caused by measurement error, as mentioned previously. The significantly greater treatment effects for spasticity, favouring the Kneehab group, are to be expected, as they received an additional intervention aimed at spasticity. In terms of the significant differences in treatment effects for HRQoL and fatigue, differences in exercise volume completed have been proposed. However, the small differences in the volumes of exercise completed versus the large difference in improvements for HRQoL and fatigue do not seem to equate. Therefore, the placebo effect of perceiving a greater improvement or starting at a higher level of HRQoL and fatigue, may account for the significant differences on these measures.

Nonetheless, the significant differences in outcomes favouring the Kneehab group are of clinical relevance, despite the trend of baseline differences, as there

was a consistently greater improvement in outcomes in the Kneehab group. This suggests that adding a NMES device, such as the Kneehab, to a PRT programme results in better outcomes compared to PRT alone. However, the mechanisms in which these greater effects occur are not fully understood.

5.5.5 Difference in Intervention Participation Between Groups

The Kneehab group demonstrated significantly higher intervention participation than the PRT group for total and quadriceps work from 6-12 weeks of intervention, and for quadriceps work and sessions completed from 0-6 weeks. In addition, there was a strong trend for the Kneehab group to complete more repetitions than the PRT group. This may be explained by the previous assertions regarding the Kneehab group starting with higher isometric strength and quadriceps endurance, which meant that they could perform more repetitions at higher workloads before fatiguing. A second possible reason for the Kneehab group completing more exercise may be due to the fact that this group had an adjunct to exercise, which may have resulted in higher motivation to exercise. Although, this was not measured, a similar effect has been shown for the incorporation of pedometers in physical activity programmes, where participants adhered to the programme better than those who did not have a pedometer (Bravata et al. 2007). In another study, participants who received home exercise equipment adhered to the exercise protocol after completion of the study compared to those who did not receive the equipment (Jakicic et al. 1999). Conversely, as participants could not be blinded to group allocation, participants in the PRT group may have completed less exercise due to demotivation at not receiving the device. Future studies should investigate if a placebo effect is the cause for greater exercise completion, as this could enhance the treatment effects participants achieve, at limited extra time and financial cost to the health service providers.

5.5.6 Limitations of Results

The primary limitation of this pilot study is the limited generalisability of the results due to a small sample which was highly variable on all outcome measures. This had the effect of reducing the certainty of treatment effects. By

using a large sample, variability is likely to be reduced, resulting in greater certainty of treatment effects. The unsupervised nature of the intervention, which has been identified as an important factor in PRT (Dalgas et al. 2008), may have had an influence on the intensity of training, thereby reducing potential treatment effects. Similarly, the contact time with stimulation was lower than what has previously been reported in the stroke literature (Glinsky et al. 2007), where significant strength increases were demonstrated. The limited amount of training (45 minutes) participants received at the start of the study may also have influenced their ability to perform the PRT to the correct intensity. Furthermore, the quality of HHD dynamometry in terms of reliability and sensitivity to change is questionable. This may have resulted in inaccurate measurement of strength. Finally, 3 participants group allocation was revealed to the study assessor, which limits the internal validity of the results. This may have affected the assessor's evaluation of these participants on certain measures. In future studies, this may be overcome by using an independent researcher to ring participants on a weekly basis.

5.6 Conclusion

In conclusion, this pilot study indicates that implementing a PRT programme in the home setting was well tolerated and feasible for PwMS who use a walking aid. The addition of the device was well tolerated in participants who did not have issues with spasticity due to hypersensitivity. The treatment effects seen in this pilot study suggest that adding an NMES device to a PRT programme improves a number of important clinical outcomes for PwMS at an equal or greater level than PRT alone. Future studies should focus on using larger cohorts, longer initial teaching of the programme, programmes where NMES stimulation time can be increased, and isokinetic dynamometry to evaluate strength.

CHAPTER 6 – PARTICIPANT SATISFACTION WITH THE KNEEHAB DEVICE

6.1 Introduction

The international trend of moving health-care towards the home setting has resulted in increased use of remote monitoring and intervention devices (Mykityshyn et al. 2002). As these devices are being used by people that are often physically or cognitively impaired by their condition, it is vital to evaluate user satisfaction with the device, particularly in terms of usability. Lehoux (2004) describes device usability as a “smooth fit” between human, technological and setting factors. In the present study, this refers to how easy it was for participants to use the Kneehab device in the home setting. Furthermore, the perceived value that a participant attributes to using a device is also an important aspect of user satisfaction. A device that is considered to provide greater therapeutic benefit is likely to be used with greater compliance.

6.2 Aims and Objectives

The aim of this chapter was to investigate participants’ satisfaction with using the Kneehab device. The objectives were:

1. To determine participants’ rating of the usability (ease of use) of the Kneehab device.
2. To determine participants’ rating on the value of using the Kneehab device.

6.3 Methods

6.3.1 Questionnaire Development

A Likert scale questionnaire was developed to evaluate participants’ satisfaction with the Kneehab device (**Appendix 13**). A five category response scale was

chosen as it has been shown to be optimal in terms of respondent preference and ease of use (Preston and Colman 2000). Preston and Colman (2000) also noted that a scale with too few categories may miss important differences, while a scale with greater than 5 categories may lead to confusion. Avoiding confusion was considered particularly important for participants in the present study due to the cognitive issues associated with MS (Noseworthy et al. 2000).

The descriptors selected for the 5 response categories were based on quantitative evaluation of descriptor meanings (Braunsberger and Gates 2009). According to the findings of Braunsberger and Gates (2009), the terms “generally agree” (1.67), “definitely agree” (3.32) and “generally disagree” (-1.74), “definitely disagree” (-3.45), demonstrated the most equal intervals while maintaining similar terminology. “Neither agree or disagree” had a mean value of 0, indicating participants considered this to be the optimal term to express neutral opinion on a statement.

In developing the statements to be used, it was considered important to avoid confusion by using a mix of positive and negative statements (Benson and Hocevar 1985). Therefore, positive statements only were used. Although this may have introduced a bias in the questionnaire, negatively phrased statements have been shown to reduce validity of the questionnaire due to inaccurate responses (Benson and Hocevar 1985).

In evaluating participants’ satisfaction with the Kneehab device, participants’ opinions on the usability and value of having the device were of interest. Since the device was used without direct supervision, statements relating to the usability of the device in terms of putting it on and taking off, and operating the controller, were developed. A statement relating to the comfort of the stimulation was considered important, in terms of usability, as this was likely to be a determining factor in whether participants would use the device or not. Finally, the ease of device use with active exercises in standing and sitting was of interest, as this would indicate whether participants felt the device was feasible to use with active exercises. The value of having the device was investigated by using a statement relating to the benefit participants felt they

received from having the device, and whether having the device motivated participants to do the exercises. Thus, the satisfaction questionnaire contained 6 items.

A section was also provided at the end for participants to make any additional comments relating to using or having the device. This was aimed at gaining feedback on aspects the questionnaire did not cover and which were relevant to participants.

6.3.2 Administering Questionnaire

The blinded assessor asked all participants following the final assessment which group they were allocated to. Participants in the Kneehab group were requested to fill out the satisfaction questionnaire. The questionnaires were completed and given to the assessor.

6.3.3 Data analysis

The questionnaire data were analysed by calculating the percentage of each response to each item. Summing of the questionnaire scores to calculate a mean score for satisfaction was not deemed appropriate as the data were ordinal. Therefore, the responses cannot be considered equidistant as with interval data (Sapsford and Jupp 1996).

6.4 Results

6.4.1 Usability of the Kneehab Device

All participants agreed that the Kneehab device was easy to put on and take off (**Figure 32**). Fourteen (93.7%) of the participants were in definite agreement and 1 (6.7%) participant was in general agreement.

The participants' all agreed that the controller of the Kneehab device was easy to use (**Figure 33**). Twelve (80%) of the participants were in definite agreement and 3 participants (20%) were in general agreement with this statement.

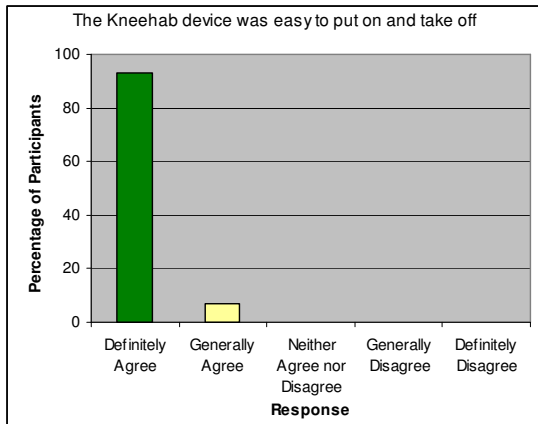


Figure 32 Participants' Response to Question 1

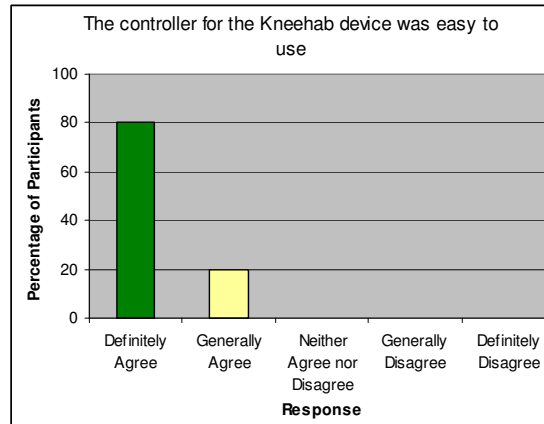


Figure 33 Participants' Response to Question 2

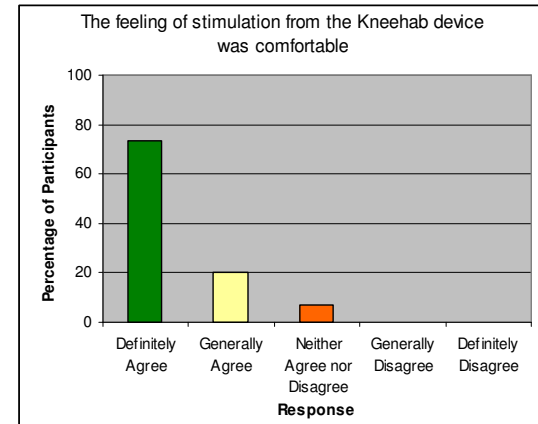


Figure 34 Participants' Response to Question 3

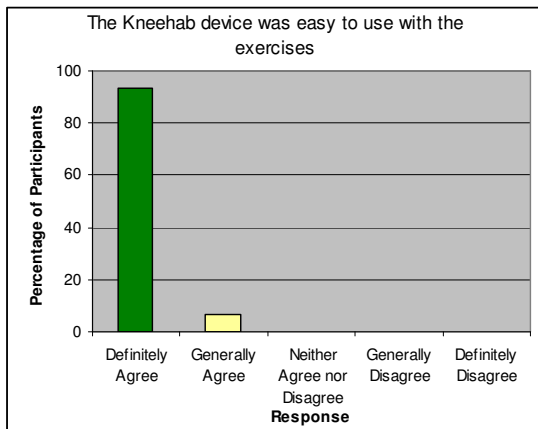


Figure 35 Participants' Response to Question 4

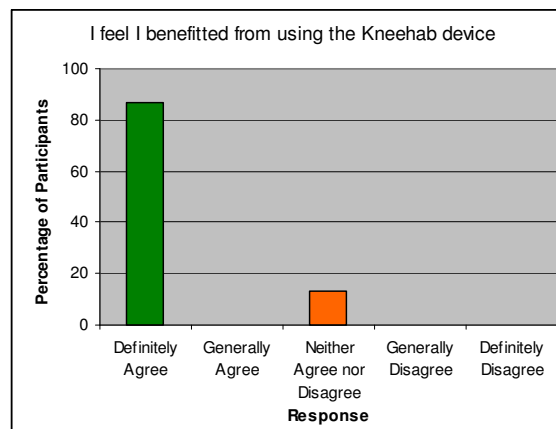


Figure 36 Participants' Response to Question 5

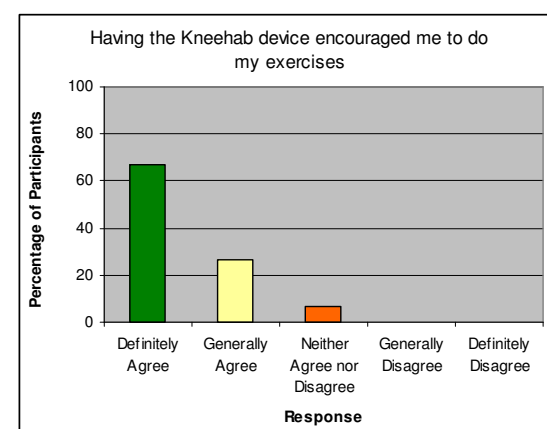


Figure 37 Participants' Response to Question 6

Eleven (73.3%) participants were in definite agreement that the feeling of stimulation from the Kneehab device was comfortable (**Figure 34**). Three (20%) participants were in general agreement, while 1 (6.7%) participant neither agreed nor disagreed with this statement.

All participants agreed the Kneehab device was easy to use with the exercises (**Figure 35**). Fourteen (93.3%) participants were in definite agreement and 1 (6.7%) participant generally agreed with this statement.

6.4.2 Value of Using the Kneehab Device

Thirteen (86.7%) participants definitely agreed that the Kneehab device benefitted them (**Figure 36**). Two (13.3%) participants neither agreed nor disagreed with this statement. On a subsequent review of the results for these 2 participants, it was found that their outcome was substantially worse by 9 and 23 points respectively on the MSWS-12 compared to the median for the Kneehab group.

Ten (66.7%) participants were in definite agreement that the Kneehab device encouraged them to do their exercises (**Figure 37**). Four (26.7%) participants were in general agreement with this statement, while 1 (6.7%) participants neither agreed or disagreed.

6.4.3 Comments

Two participants offered comments on the device.

One participant said:

“The wire was often in the way. A remote system would be better.”

The second participant felt:

“The waiting time [off period of stimulation] is too long for the squats and all standing exercises. A program with 3-5 second intervals would be better.”

6.5 Discussion

The primary aim of this chapter was to determine participant satisfaction with the Kneehab device. Previous studies of user satisfaction with electrical stimulation devices have focused on functional electrical stimulation systems (Taylor et al. 1999, Taylor et al. 2001). Therefore, this study provides new insights into participant satisfaction with a NMES device. The results demonstrated a generally high level of satisfaction amongst participants with the usability and therapeutic value of the Kneehab device. However, this positive impression of the device must be viewed with caution, as the questionnaire was answered in the presence of the assessor and only positive statements were used. Consequently, participants may have responded in a more positive light. Additionally, the sample size was small.

6.5.1 Usability of Kneehab Device

The majority of participants were in agreement that applying the Kneehab device to the thigh was not difficult and that the controller was easy to operate. Only one participant felt that the wire of the device was obstructive at times. The pre-placed electrodes are likely to have contributed the ease of application and general use, as this was previously reported as an issue with an FES system (Taylor et al. 1999). In addition, the design of the Kneehab device with guidance markers for placement above the knee and Velcro straps are important features for ease of application. For PwMS, these aspects are of clinical relevance if an electrical stimulation device is to be used in a non-supervised setting, due to the upper limb disability associated with MS (Thompson and Hobart 1998). Furthermore, the initial training in device use may have played an important role in the ability of participants to use the device effectively. Education and training in the use of medical devices in the home setting has been identified as important to ensure correct and adequate use (Lehoux 2004).

Participant satisfaction with the use of the Kneehab device with the exercises indicates that superimposing stimulation on functional exercises was both feasible and safe. A difficulty mentioned by one participant was the length of

the off phase of stimulation between contractions, which in future studies may be worth modifying in order to reduce the length of standing time, and time for recovery. Generally, participants were in agreement that the stimulation was comfortable. Taylor et al. (2001) also found that participants using an implanted upper limb FES system found the stimulation comfortable. In the present study, this may be attributed to the enhanced comfort that the manufactures purport with the Multipath ® system (Bio-Medical Resaerch Ltd. 2011), or the use of large surface electrodes, which reduce current density (Baker and Parker 1986). The fact that participants were advised to set the intensity at their maximally tolerable level may have reduced the level of discomfort they experienced. Regardless, the clinical implication is that due to perceived stimulation comfort, users of the device are likely to be more compliant.

6.5.2 Perceived Value of Using the Kneehab Device

The majority of participants were in strong agreement that using the Kneehab device was valuable in terms of benefits gained and encouragement to complete the exercises. The specific nature of the benefit participants perceived from using the device is unclear, however, as the questionnaire did not investigate this aspect. The results of **Chapter 5** suggest that the clinical benefits may have included improved balance, muscle endurance, spasticity, HRQoL and fatigue.

The encouragement participants felt the Kneehab device provided to complete their exercises is important, due to the clinically recognised issues with low compliance in home exercise programmes. The completion of a higher volume of exercise by the Kneehab participants compared to the PRT group, supports the role of the device as a motivation to comply with the programme. Similar results have been shown with the use of pedometers in physical activity programme and home exercise equipment (Bravata et al. 2007, Jakicic et al. 1999). This supports the view that adding a device to an exercise intervention increases compliance.

6.5.3 Limitations

The two main limitations of these results are the small sample size and the design of the questionnaire. The questionnaire did not incorporate triangulating questions, to determine if participants responded consistently to a concept regardless of the positive or negative phrasing of the question. As a result, participants' responses may have been biased with the use of positively phrased questions only. Participants' responses may also have been biased to favour a positive response as the study assessor was present when the questionnaire was answered.

6.6 Conclusion

In conclusion, these results indicate that participants are generally satisfied with the usability of the Kneehab device, and it may have had a positive influence on their compliance with the intervention. This assertion needs to be confirmed in future research. In addition, future studies investigating NMES device satisfaction in this population need to utilise larger cohorts, administer the questionnaire by an independent researcher, use triangulating questions and questions that are more specific on design aspects and therapeutic benefits gained.

CHAPTER 7 – CONCLUDING DISCUSSION

7.1 Thesis Overview

In this thesis the aims were to:

1. Review clinical profile, PRT and NMES literature for PwMS who use a walking aid.
2. Investigate the clinical profile of PwMS who use a walking aid.
3. Evaluate the effects of adding an NMES device to a home-based PRT programme for PwMS who use a walking aid.
4. Investigate participants' satisfaction with the usability of the NMES device.

In the first part of the literature review it was found that previous investigations of the clinical profile of PwMS have not included an analysis of PwMS who use a walking aid. Nonetheless, a number of clinical problems experienced by PwMS, which impact upon their ability to perform daily activities, were identified. However, the relationships between these clinical problems, specifically measures of strength and function, have not been well established in the MS population.

The review of the PRT and NMES research revealed that none of the studies included PwMS who use a walking aid exclusively. Only one study (Broekmans et al. 2011) combined PRT and NMES. There were no reports of adverse events with either intervention, individually or combined. PRT, and to a lesser degree NMES were found to improve a number of the clinical problems associated with MS. However, the quality of the research was generally low, with a high level of bias according to the Cochrane Collaboration's tool for assessing the risk of bias. The main methodological issues were the use of a non-RCT design and failing to blind the assessors. Furthermore, considering the increasing global shift in health-care delivery towards primary care, there was a limited number of studies evaluating the use of either intervention in the home setting. Therefore,

the investigation of PwMS who use a walking aid, and combining PRT with an NMES device in the home setting, were the novel features of this thesis.

The main findings of the clinical profile study were that muscle weakness, balance and mobility limitations are more severe problems for PwMS who use a walking aid than for other neurological populations, and in less disabled MS populations. Significant associations of moderate strength between quadriceps endurance and balance, and quadriceps endurance and mobility were found. The clinical value of these associations was limited by a similar activity being measured in all tests. This may partly account for the strength of the correlations, rather than an actual correlation between the variables measured by the tests.

In the main study of the thesis, both the PRT and Kneehab groups demonstrated statistically significant improvement for balance and gluteal strength. The Kneehab group also demonstrated significant improvements in plantar-flexion strength, rectus femoris thickness, quadriceps endurance, spasticity, fatigue and HRQoL. Of these improvements, plantar-flexion strength, spasticity, fatigue and HRQoL were significantly better than in the PRT group. In addition, Kneehab participants demonstrated greater intervention participation by completing significantly more sessions, total and quadriceps work than the PRT group. Although both programmes were generally well tolerated, there were two drop-outs in the Kneehab group due to muscle spasm induced by the stimulation. This appears to be due to issues with hypersensitivity.

The higher quadriceps strength gains expected in the Kneehab group were not seen, indicating that other factors may have resulted in the greater improvements in the Kneehab group. The trend towards lower strength and muscle endurance impairment in the Kneehab group may explain why they were able to do more exercise and thus demonstrate greater improvements. Another possible reason could be a placebo type effect of having the device, which encouraged Kneehab participants to do more exercise. This is substantiated by the fact that Kneehab participants agreed that having the device encouraged them to do their exercises.

In the final study of the thesis, it was found that participants were generally satisfied with the usability and value of having the Kneehab device.

7.2 Strengths and Limitations of this Research

This research builds on existing gaps in the MS literature for clinical profiling and superimposing NMES on PRT, specifically in PwMS who use a walking aid. The main strengths of this research are in the study design. The use of two groups to compare differences in outcomes, randomisation of participants and measures to maintain blinding of the assessor, have not been widely or adequately performed in previous studies, as outlined in the literature review. Although this has the effect of improving the external validity of the results, a number of limitations restrict the generalisability of the findings to PwMS who use a walking aid, and clinical practice. One of the primary issues is the small sample size, which is likely to have resulted in the study being under-powered for certain outcomes. For example, the non-significant trends for improvement on measures of mobility and quadriceps strength may reach significance in larger cohorts. The high level of variability on clinical outcomes in this study's population may also be a reason for the lack of significant improvement on certain outcomes. Therefore, future studies need to recruit larger and more homogenous samples.

Study design issues, specifically blinding, must also be recognised as a limitation in this research. Due to a lack of resources, the assessor was also involved in monitoring and progressing participants' exercise via telephone calls. This resulted in group allocation being revealed in 3 instances. Similarly, participants were not blinded to group allocation, which may have been possible if a third group was included that used sham NMES stimulation. However, this was beyond the scope of this research.

The lack of significant treatment effects, particularly on the main outcome of quadriceps strength, may have resulted from an inadequate training stimulus from the PRT and the NMES. By supervising exercise progression remotely, participants may not have been exercising to fatigue, thereby reducing the

intensity of training. For NMES, the maximal stimulation time of 12 minutes per session may also have been insufficient to significantly improve strength. Furthermore, the stimulation parameters may have been inadequate in increasing activation of the quadriceps.

Another limitation in detecting significant treatment effects relates to the outcome measures employed. A number of limitations of strength measurement with HHD have been identified previously (Kolber and Cleland 2005). Isokinetic dynamometry is the gold standard for strength measurement (Martin et al. 2006); however, this was not feasible due to logistics and cost. For similar reasons, the development of a novel RTUS approach was used to measure muscle thickness. Errors in measurement using these outcomes may have resulted in significant changes being missed.

Finally, the user satisfaction data may also have been compromised by using positive statements only and not including triangulating questions on the questionnaire. The presence of the assessor when the questionnaire was being filled out may also have biased participants' responses. As a result the validity of the satisfaction results are reduced.

7.3 Future Research

Based on the limitations and results of this pilot research, there are a number of areas future research should investigate, in order to establish whether superimposing NMES on PRT is beneficial. First, it is important to identify whether superimposing stimulation on voluntary contraction using the Kneehab device or other such devices results in an increased force output compared to voluntary contraction alone. In undertaking such research it would also be worthwhile evaluating which NMES parameters produce the highest force output with voluntary contraction. Following on from that, in clinical studies the optimal length of stimulation time required to improve relevant outcomes, particularly strength is important to identify. The overall aim of these studies is to identify the optimal NMES protocol to improve outcomes. At this stage, comparing NMES to sham stimulation would also be appropriate to clarify

whether there is an actual treatment effect, or whether the use of an NMES device produces a placebo effect of increasing the volume or intensity of exercise. Furthermore, comparing home PRT using an NMES device with a gym supervised PRT in terms of clinical improvements and cost would also be valuable. A study of this nature would help to inform which approach provides the best clinical outcomes relative to cost.

In carrying out these clinical studies, continued use of an RCT design, with an adequate number of investigators to ensure sufficient blinding is also important. The recruitment of larger cohorts that are more homogenous in terms of impairment and disability will also be vital. In addition, the use of gold standard measures to ensure certainty of outcomes is necessary. Addressing these issues in study design is also important for future studies aiming to establish whether there is a relationship between muscle strength and function. This is a key area that requires further study. By establishing whether relationships exist, PRT programmes may be used more effectively to target functional limitations.

Finally, future research should also aim to build on the findings of the present research relating to satisfaction with NMES device usability. Specifically, the research should aim to confirm whether having a device such as the Kneehab is an influence on the completion of more exercise. This important to understand as it may be a useful way of increasing the volume of rehabilitation PwMS receive.

7.4 Conclusion

In conclusion, the literature review found that PwMS experience a variety of clinical problems, and the relationships between these problems are not well established. The literature review also identified a lack of high-quality evidence supporting the use of PRT and NMES, individually or combined, in PwMS who use a walking aid. The clinical profile study found that muscle weakness, balance and mobility limitations were severe problems in our cohort. This indicated the need for targeted rehabilitation of these problems. The clinical value of the moderate associations shown between quadriceps endurance and

balance, and quadriceps endurance and mobility, are limited by issues with the outcome measures. The randomised study comparing home-based PRT to the same with the Kneehab device, found that both were safe and generally well tolerated, although NMES may not be suitable for those with sensory hypersensitivity that elicits muscle spasm. In terms of clinical outcomes, participants in both groups demonstrated improvements; however, overall the Kneehab group showed greater improvement, which was significant for some outcomes. This may be partly due to a placebo effect of having the NMES device, as there was a non-significant increase in the main outcome of quadriceps strength, yet the Kneehab group completed significantly higher volumes of exercise. Participants who received the device may have been motivated to complete more exercise due to having the device. This is substantiated by the high level of satisfaction with the usability and value of having the device. The indication is that the design of the device was suitable for unsupervised home use. The generalisability of these results is restricted due to limitations in the study design and intervention protocol. Suggestions for future directions of research are made, which may help to confirm whether superimposing NMES on voluntary contractions during PRT in the home setting is beneficial for PwMS who use a walking aid.

APPENDICES

Appendix 1 – Expanded Disability Status Scale

0.0	Normal neurological examination
1.0	No disability, minimal signs in one Functional System (FS)
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self care functions
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

Appendix 2– Participant Consent Form



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Participant Consent Form

Title of Study:

An Evaluation of the Effects of Augmenting Quadriceps Strengthening in People with Multiple Sclerosis using Neuromuscular Electrical Stimulation

Investigators:

Dr. Susan Coote	E-mail Address: susan.coote@staffmail.ul.ie	Tel: 061-234278
Mr. Lonan Hughes	E-mail Address: lonan.hughes@staffmail.ul.ie	Tel: 061-233768
Prof. Alan Donnelly	Email Address: alan.donnelly@staffmail.ul.ie	Tel: 061-202808
Mr. Gary Rainsford	Email Address: grainsford@bmr.ie	Tel: 091-774300

My signature indicates that I have read and understood the information leaflet and all my questions regarding my participation have been answered satisfactorily. I am aware of my role in participating and that participation is entirely voluntary and that I may withdraw at any stage. By signing this consent form I am giving permission for the data collected from me to be used as part of this study.

Signature of Research Participant

Date

Printed Name of Research Participant

Date

Signature of Researcher

Date

Printed Name of Researcher

Date

Appendix 3 – Information Leaflet



UNIVERSITY of LIMERICK
OLLSCOIL LUIMNIGH

Subject Information Leaflet

Title of study:

An Evaluation of the Effects of Augmenting Quadriceps Strengthening in People with Multiple Sclerosis using Neuromuscular Electrical Stimulation

Background:

Research studies have shown that strengthening exercise programs for people with MS can improve their muscle strength and their ability to do daily activities. Other studies have shown that electrical stimulation of the muscles can also improve strength gains. To date no studies have looked at trying to improve strength and daily function in people with MS by adding an electrical stimulation device to a strengthening program.

What would you have to do?

Taking part in this study will involve completing a 12 week home exercise program to strengthen your legs. A researcher will come to your house on an agreed date and time to test your strength, balance, walking ability and give you 3 questionnaires to fill out. The researcher will then teach you the exercise program and give you a booklet with written information and diagrams of how to do the exercises. The exercise program has 6 exercises and the difficulty of the exercises will be tailored to your ability. You will also be given a diary to keep track of your exercises.

You will then be contacted within 1 week to inform you if you have been randomly chosen to continue with this exercise program or if you will be receiving the additional electrical stimulation. If you are to receive the device a

physiotherapist will come out to your house to teach you how to use it on your weaker side with the exercises you have already been given.

The electrical stimulation device is called KneeHab. It is made of stretchy material like a wetsuit that wraps around your thigh, and has the electrical pads already in place so it is easy to put on. You will not feel an electric shock, only a comfortable tingling sensation and you can control how strong it is.

On a weekly basis you will receive a phone-call to check on your progress and advise you on how to progress the exercises. The researcher will return 6 weeks into your program and at the end to test the same things that were tested with you at the start.

What are the criteria for taking part?

If you are interested in participating in this study there are a few criteria you must meet. You must:

1. Have a confirmed diagnosis of MS by a consultant neurologist
2. Use any type of walking aid (stick, crutch or frame)
3. Not have a pacemaker or metal implant in your legs
4. Not have a current injury to your knee or thigh
5. Have full and normal feeling in your legs
6. Not be participating in an exercise program currently or in the last month and
7. Not have an increase in your symptoms currently.

What are the potential benefits and risks of taking part?

The research has shown that potential benefits of strengthening programs are:

1. Improved muscle strength
2. Improved balance and ability to walk
3. Decreased levels of fatigue

The research has shown that some potential risks with strengthening exercise are:

1. Muscle soreness due to exercise or the device, which may last for 2-3 days
2. A possible increase in symptoms (muscle tone and fatigue) that is temporary, lasting less than one day with no long-term consequences

Confidentiality:

In order to ensure that any information recorded is kept confidential; you will be given a code that will be used in place of your name on all data sheets and forms. In addition, all data will be stored in a locked cabinet in the University of Limerick.

If you wish to participate or have any further questions regarding this study please contact the researchers.

There is no obligation to participate in this study but if you are interested please contact the researchers at the details listed below. In addition, as participation is voluntary if you decide at any stage that you wish to withdraw your participation and use of your data from the study, you are entitled to do so and there will be no repercussions. Please contact the researcher to inform them if this occurs.

Researchers:

Dr. Susan Coote Email Address: susan.coote@staffmail.ul.ie

Tel: 061-234278

Mr. Lonan Hughes E-mail Address: lonan.hughes@staffmail.ul.ie

Tel: 061-233768

If you have concerns about this study and wish to contact someone independent, you may contact:

*The Chairman of the Education and Health Sciences Research Ethics
Committee,
University of Limerick,
Limerick.
Tel: (061) 234101*

Appendix 4 – Exercise Booklet

Thank you for offering to participate in this research project.

When the researcher (Lonan Hughes) is finished today you should start the exercises as soon as possible (tomorrow or the day after). You will continue with the exercises for 12 weeks. You may receive a phone-call in the next few days to inform you that you are to receive the Kneehab device. If so another researcher (Gary Rainsford) will come to your home to teach you how to use the Kneehab with the exercise programme.

We do not know if adding this type of device gives extra benefits compared to exercise alone. For this reason it is important to continue with the exercises as normal if you do not get a phone-call.

Lonan will return 6 weeks into the programme and at the end to do the physical tests and questionnaires with you again. You will also receive weekly phone calls from Lonan to check on how you are doing with the exercises, to answer any questions you have and to give you advice on how to progress your exercises.

This booklet will help to guide you through the steps of completing the home strengthening programme that is part of the research project. The booklet contains:

- An explanation of the exercise programme
- Written descriptions and pictures of how to perform the exercises
- Details of how to progress the exercises
- Instructions on how to fill out the exercise diaries and
- Exercise diaries to record your progress.

Before you start the programme remember that you may experience a temporary worsening of your symptoms following the exercise. This is known as Uhtoff's phenomenon. It happens because of your body's increased temperature with exercise. For most people this worsening of symptoms lasts for 30 minutes or less after exercise.

If you experience pain or an increase in your symptoms for longer than this period you should contact the researchers immediately to inform them. To reduce the risk of this happening you should exercise with a window open, a fan turned on or drink ice cold water during exercise.

If you have any difficulties or urgent questions please contact the researchers below.

Mr. Lonan Hughes	E-mail Address: lonan.hughes@staffmail.ul.ie Tel: 061-233768
Dr. Susan Coote	Email Address: susan.coote@staffmail.ul.ie Tel: 061-234278

The Exercise Program

There are 6 exercises in this exercise programme. All 6 of these exercises should be done twice a week for the first 6 weeks and 3 times a week for the second 6 weeks.

Four of the exercises work the muscles at the front of the thigh. The order of the exercises is designed so that these muscles are given a rest between other exercises and the less tiring exercises are at the end. For this reason **you should do the exercises in the order they are described every time.** This will stop your muscles from tiring too much.

The Exercises

Before you start the exercises set up your chair beside where you will exercise. This will give you a place to rest during your exercise.

Exercise 1 (Squats):

1. Stand in the Start Position.
2. Your heels should be on the ground and you should not be bent forward at the hips. Hold onto a counter-top, table or window-sill for support.
3. Hold for 5 seconds.



Start



End Position

4. **Slowly** stand up to the End Position. This is 1 repetition completed.
5. After 5 seconds start the next repetition by **slowly** bending your knees.
6. **Try and complete 12 repetitions. This is a full set.**
7. Take a rest for 2-3 minutes.
8. If you did 12 repetitions start a second set, if not move onto the next exercise.

Progression:

- When you can complete 1 set without tiring use only 1 hand for support.
- When you are safe and steady with one hand and can complete 2 sets without tiring start using no hands.
- When you are not tired after 3 sets without support hold weights or items in your hands such as tins of beans. Lonan will advise you on the amount of weight to use in the phone-calls.

Exercise 2 (Calf-Raises):

1. Stand in the Start Position. Hold onto a counter-top, table or window-sill for support.

2. **Slowly** push up onto your toes keeping your knees straight (End Position).



Start



End Position

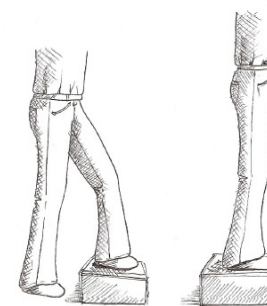
3. Hold this position for 3 seconds.
4. Lower your feet back to the ground (Start Position). This is 1 repetition.
5. **Try and complete 12 repetitions. This is a full set.**
6. Take a rest for 2-3 minutes.
7. If you did 12 repetitions start a second set, if not move onto the next exercise.

Progression:

- When you can complete 1 set without tiring use only 1 hand for support.
- When you are safe and steady with one hand and can complete 2 sets without tiring start using no hands.
- When you are not tired after 3 sets without support hold weights or items in your hands such as tins of beans. Lonan will advise you on the amount of weight to use in the phone-calls.

Exercise 3 (Step-ups):

1. Stand in the Start Position with your weaker leg on the step or wooden box. Hold onto a banister or chair for support.
2. **Slowly** step up to the End Position.



Start

End Position

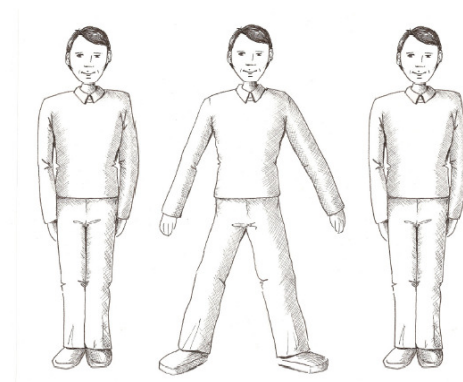
3. Hold this position for 5 seconds.
4. **Slowly** return to the Start Position. This is 1 repetition completed.
5. Rest for 5 seconds and start again.
6. **Try and complete 12 repetitions. This is a full set.**
7. Take a rest for 2-3 minutes.
8. If you did 12 repetitions start a second set, if not move onto the next exercise.

Progression:

- When you can complete 1 set without tiring use only 1 hand for support.
- When you are safe and steady with one hand and can complete 2 sets without tiring start using no hands.
- When you are not tired after 3 sets without support hold weights or items in your hands such as tins of beans. Lonan will advise you on the amount of weight to use in the phone-calls.

Exercise 4 (Side-Stepping):

1. Standing at a table or counter-top for support if necessary.
2. Take a side-step to your right. Then take a side-step back to your left.
This is 1 repetition.



3. **Try and complete 12 repetitions. This is a full set.**

4. Take a rest for 2-3 minutes.
5. If you did 12 repetitions start a second set, if not move onto the next exercise.

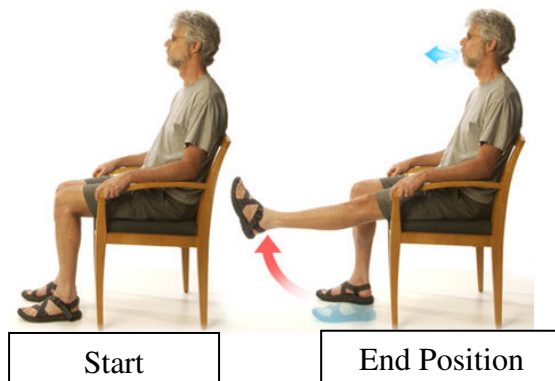
Progression:

- When you can complete 1 set without tiring use only one hand for support.
- When you are safe and steady with one hand and can complete 2 sets without tiring start using no hands.

- Once you are steady with no hands you should take 2 and then 3 side-steps in each direction. Increase the number of side-steps when you can do 3 sets without tiring.
- When you are not tired after 3 sets without support hold weights or items in your hands such as tins of beans. Lonan will advise you on the amount of weight to use in the phone-calls.

Exercise 5 (Knee Extensions):

1. Sit in the Start Position.
2. Straighten your weaker knee **slowly** by lifting your foot into the air (End Position).



3. Hold this position for 5 seconds.
4. **Slowly** return to the Start Position. This is 1 repetition complete.

5. Try and complete 12 repetitions. This is a full set.

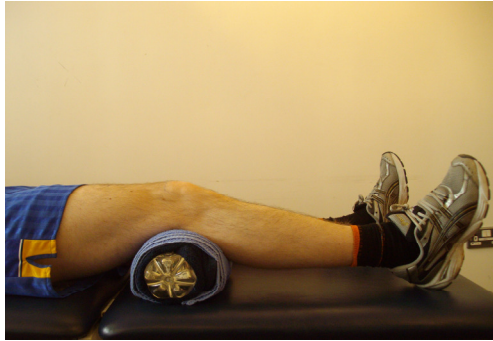
6. Take a rest for 2-3 minutes.
7. If you did 12 repetitions start a second set, if not move onto the next exercise.

Progression:

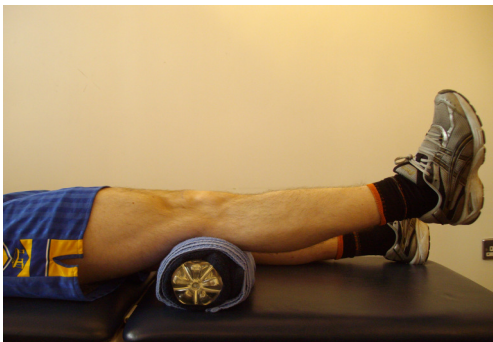
- When you can do 3 sets without tiring add weight to your ankle. This can be done using ankle weights from a sports shop, or by putting everyday items i.e. tins of food, in a bag or stocking and tying them to your ankle. Lonan will advise you on the amount of weight to use in the phone-calls.

Exercise 6 (Inner Range Quads):

1. Lie in the Start Position with a 2 litre bottle of water wrapped in a towel under the back of your weak knee.
2. **Slowly** straighten your knee (End Position).
3. Hold this position for 5 seconds.
4. **Slowly** return to the Start Position.



Start



End Position

Progression:

- When you can do 3 sets without tiring add weight to your ankle. This can be done using ankle weights from a sports shop, or by putting everyday items i.e. tins of food, in a bag or stocking and tying them to your ankle. Lonan will advise you on the amount of weight to use in the phone-calls.

5. **Try and complete 12 repetitions. This is a full set.**
6. Take a rest for 2-3 minutes.
7. If you did 12 repetitions start a second set.

Appendix 5 – Instructions on Using the Kneehab Device

Placing and Changing Electrical Pads

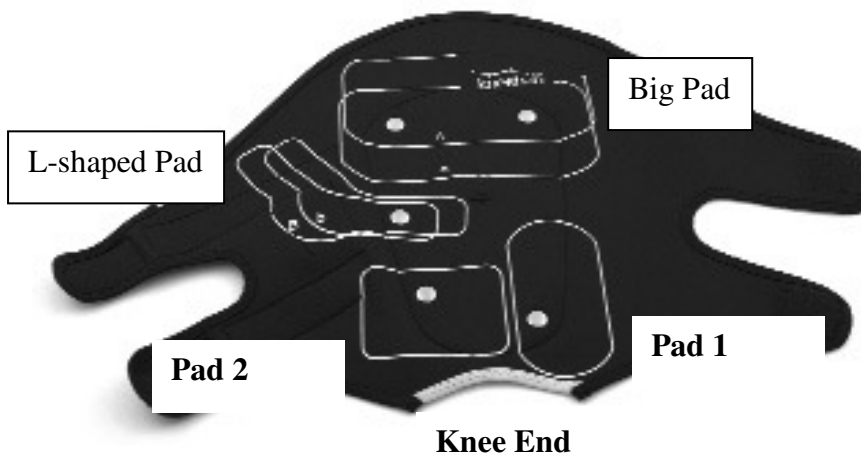
The pads on the Kneehab device have been placed suitable for your height and size. You should not change their position.

You have been given three sets of pads. It is likely that you will only need to change them once after 6-8 weeks of the programme. You should change the pads if:

- The tingling feels very low at high intensities
- The pads are not sticking well to the garment and
- The surface of the pads appears worn.

When changing the pads you should:

- Place pads 1 and 2 at the knee end.
- Place the biggest pad over the **small a** **BIG A**.
- Place the L-shaped pad over the **small b** **BIG B**.
- The metal studs should be completely covered by the pads.



Putting on the Kneehab Device

Before putting the device on check to make sure:

- The battery is fully charged and
- The surface of the pads is not worn

To put on the device:

- Sit on the edge of a seat with your _____ leg straight in front of you. You should only put the Kneehab on this leg.

- Place the Kneehab on your thigh with the light blue end above your kneecap. The mid-line should be over the centre of your thigh.
- Fasten the Velcro straps. Bend and straighten your knee a few times to make sure the Kneehab is not too loose or tight.

Using the Kneehab Device

Before you start the exercises set the intensity of the device to a maximally tolerable level. This should **always** be done in sitting, beside where you are going to exercise.

The buttons of the programming device:

- To turn the device on and off hold the on/off button for 2 seconds or more.
- To pause and restart the device, press the on/off button once.
- To turn the intensity up and down press the up and down arrows.
- The “P” button is to change the programme. The programme should always be on 1. **You should not press this button.**
- The unit display shows you the intensity level that is set for right and left sides.



Programming Device

Appendix 6 – Baseline Normality Whole Group

Outcome Measure	Shapiro-Wilk Value
Quadriceps Strength Weak Side	0.126
Plantar-flexor Strength Weak Side	0.665
Gluteal Strength Weak Side	0.010*
Lower Limb Extensor Strength Weak Side	0.177
Quadriceps Strength Strong Side	0.222
Rectus Femoris Thickness Weak Side	0.994
Vastus Intermedius Thickness Weak Side	0.020*
Total Quadriceps Thickness Weak Side	0.201
Rectus Femoris Thickness Strong Side	0.327
Vastus Intermedius Thickness Strong Side	<0.01*
Total Quadriceps Thickness Strong Side	0.008*
Quadriceps Endurance (with Outlier)	<0.01*
Quadriceps Endurance (without Outlier)	<0.01*
Spasticity	0.207
Balance (Berg)	0.120
Mobility (TUG)	<0.01*
Mobility (MSWS-12)	<0.01*
Fatigue (MFIS physical + social)	0.055
Fatigue (MFIS cognitive)	0.122
Quality of Life (MSIS-29 physical)	0.345
Quality of Life (MSIS-29 psychological)	0.036*

* : denotes outcome being non-normally distributed.

Appendix 7 – Normality Values PRT and Kneehab Groups

Original Score

Outcome / Variable	Week 0		Week 6		Week 12	
	PRT	Kneehab	PRT	Kneehab	PRT	Kneehab
Quadriceps Strength Weak Side	0.558	0.880	0.785	0.319	0.350	0.376
Plantar-flexor Strength Weak Side	0.479	0.951	0.762	0.958	0.995	0.991
Gluteal Strength Weak Side	0.984	0.270	0.539	0.374	0.109	0.433
Rectus Femoris Thickness Weak Side	0.942	0.106	0.951	0.845	0.984	0.494
Vastus Intermedius Thickness Weak Side	0.232	0.832	0.095	0.611	0.186	0.486
Quadriceps Endurance	<0.001*	0.009*	<0.001*	0.013*	0.247	0.048*
Spasticity	0.812	0.186	0.534	0.002*	0.963	0.001*
Balance (Berg)	0.691	0.088	0.012*	0.441	0.129	0.006*
Mobility (TUG)	0.171	0.001*	0.026*	0.008*	0.022*	0.265
Mobility (MSWS-12)	0.005*	0.183	0.518	0.304	0.287	0.253
Quality of Life (Total)	0.564	0.726	0.022*	0.868	0.414	0.224
Quality of Life (Physical Subscale)	0.518	0.545	0.058	0.730	0.858	0.297
Quality of Life (Psychological Subscale)	0.410	0.285	0.109	0.011*	0.162	0.003*
Fatigue (Total)	0.270	0.989	0.247	0.470	0.125	0.216

*** : denotes outcome being non-normally distributed**

Change Score

Outcome / Variable	Change 0-6		Change 6-12		Change 0-12	
	PRT	Kneehab	PRT	Kneehab	PRT	Kneehab
Quadriceps Strength Weak Side	0.249	0.679	0.286	0.513	0.850	0.963
Plantar-flexor Strength Weak Side	0.740	0.486	0.805	0.545	0.861	0.961
Gluteal Strength Weak Side	0.574	0.823	0.105	0.127	0.652	0.192
Rectus Femoris Thickness Weak Side	0.208	0.138	0.978	0.177	0.478	0.731
Vastus Intermedius Thickness Weak Side	<0.001*	0.672	0.081	0.917	0.022*	0.342
Quadriceps Endurance	0.559	0.007*	<0.001*	<0.001*	0.048*	0.005*
Spasticity	0.543	0.227	0.103	0.007*	0.303	0.112
Balance (Berg)	0.437	<0.010*	0.993	0.103	0.152	0.342
Mobility (TUG)	0.003*	<0.001*	0.919	0.815	0.078	<0.001*
Mobility (MSWS-12)	0.028*	0.827	0.837	0.116	0.904	0.449
Quality of Life (Total)	0.709	0.129	0.605	0.239	0.038*	<0.001*
Quality of Life (Physical Subscale)	0.681	0.585	0.658	0.280	0.189	0.015*
Quality of Life (Psychological Subscale)	0.733	0.031*	0.047*	0.021*	0.296	0.021*
Fatigue (Total)	0.783	0.318	0.016*	0.083	0.049*	0.318

*** denotes outcome being non-normally distributed**

Appendix 8 – PASW Output for Comparison of Baseline Differences

Independent T-Test Output:

		Independent Samples Test								
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	T	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Quadriceps Strength Weak Side Time 1	Equal variances assumed	.037	.850	-1.326	23	.198	-24.05733	18.13830	-61.57927	13.46460
	Equal variances not assumed			-1.328	19.538	.199	-24.05733	18.11254	-61.89673	13.78206

Mann Whitney U Test Output:

Test Statistics ^b	
	T1
Mann-Whitney U	69.500
Wilcoxon W	124.500
Z	-.305
Asymp. Sig. (2-tailed)	.760
Exact Sig. [2*(1-tailed Sig.)]	.765 ^a
Exact Sig. (2-tailed)	.775
Exact Sig. (1-tailed)	.387
Point Probability	.010

****Numbers highlighted in bold are p-values of interest for the respective tests.**

Appendix 9 – PASW Output for Within Group Analysis

One Way Repeated Measures of ANOVA

Mauchly's Test of Sphericity^b

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	Df	Sig.	Epsilon ^a		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Rectus Femoris Weak Side	.997	.021	2	.990	.997	1.000	.500

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b. Design: Intercept

Within Subjects Design: RectusFemorisWeakSide

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Rectus Femoris Weak Side	Sphericity Assumed	.012	2	.006	.801	.464
	Greenhouse-Geisser	.012	1.995	.006	.801	.464
	Huynh-Feldt	.012	2.000	.006	.801	.464
	Lower-bound	.012	1.000	.012	.801	.394
Error (Rectus Femoris Weak Side)	Sphericity Assumed	.139	18	.008		
	Greenhouse-Geisser	.139	17.954	.008		
	Huynh-Feldt	.139	18.000	.008		
	Lower-bound	.139	9.000	.015		

Post-Hoc Analysis (Bonferroni):

Pairwise Comparisons

Measure: MEASURE_1

(I) Rectus Femoris Weak Side	(J) Rectus Femoris Weak Side	Mean Difference (I-J)	Std. Error	Sig. ^a	95% Confidence Interval for Difference ^a	
					Lower Bound	Upper Bound
1	2	.044	.039	.855	-.070	.158
	3	.002	.040	1.000	-.116	.120
2	1	-.044	.039	.855	-.158	.070
	3	-.042	.039	.922	-.156	.072
3	1	-.002	.040	1.000	-.120	.116
	2	.042	.039	.922	-.072	.156

Based on estimated marginal means

a. Adjustment for multiple comparisons: Bonferroni.

****Numbers highlighted in bold are p-values and 95% Confidence Intervals of interest.**

Friedmans Test:

Test Statistics^a

N	10
Chi-square	1.400
Df	2
Asymp. Sig.	.497
Exact Sig.	.601
Point Probability	.165

a. Friedman Test

Post-Hoc Analysis (Wilcoxon Signed Ranks Test):

Ranks

		N	Mean Rank	Sum of Ranks
Grp1Weak2 – Grp1Weak1	Negative Ranks	5 ^a	5.20	26.00
	Positive Ranks	5 ^b	5.80	29.00
	Ties	0 ^c		
	Total	10		
Grp1Weak3 – Grp1Weak2	Negative Ranks	3 ^d	4.33	13.00
	Positive Ranks	7 ^e	6.00	42.00
	Ties	0 ^f		

	Total	10		
Grp1Weak3 – Grp1Weak1	Negative Ranks	4 ^g	3.75	15.00
	Positive Ranks	6 ^h	6.67	40.00
	Ties	0 ⁱ		
	Total	10		

- a. Grp1Weak2 < Grp1Weak1
- b. Grp1Weak2 > Grp1Weak1
- c. Grp1Weak2 = Grp1Weak1
- d. Grp1Weak3 < Grp1Weak2
- e. Grp1Weak3 > Grp1Weak2
- f. Grp1Weak3 = Grp1Weak2
- g. Grp1Weak3 < Grp1Weak1
- h. Grp1Weak3 > Grp1Weak1
- i. Grp1Weak3 = Grp1Weak1

Test Statistics^b

	Grp1Weak2 - Grp1Weak1	Grp1Weak3 - Grp1Weak2	Grp1Weak3 - Grp1Weak1
Z	-.153 ^a	-1.478 ^a	-1.274 ^a
Asymp. Sig. (2-tailed)	.878	.139	.203
Exact Sig. (2-tailed)	.922	.160	.232
Exact Sig. (1-tailed)	.461	.080	.116
Point Probability	.038	.015	.020

- a. Based on negative ranks.
- b. Wilcoxon Signed Ranks Test

****Numbers highlighted in bold are p-values of interest for the respective tests.**

Appendix 10 – PASW Output for Between Group Analysis

One-Way Repeated Measures of ANOVA with a Between Groups Factor

Source	Weak	Type III Sum of Squares	Df	Mean Square	F	Sig.
Weak	Linear	.054	1	.054	2.207	.151
	Quadratic	.056	1	.056	3.553	.072
Weak * GrpAllocation	Linear	.058	1	.058	2.340	.140
	Quadratic	.004	1	.004	.261	.614
Error(Weak)	Linear	.567	23	.025		
	Quadratic	.361	23	.016		

****Numbers highlighted in bold are p-values of interest for the respective tests.**

Post-Hoc Analysis:

Independent T-Test & Mann Whitney U Test as in **Appendix 10.**

Appendix 11 – Plots of Raw Strength and Quadriceps Thickness Data

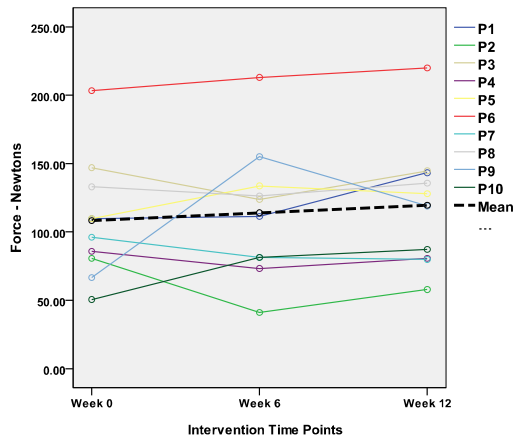


Figure 38 Quadriceps Strength PRT Group

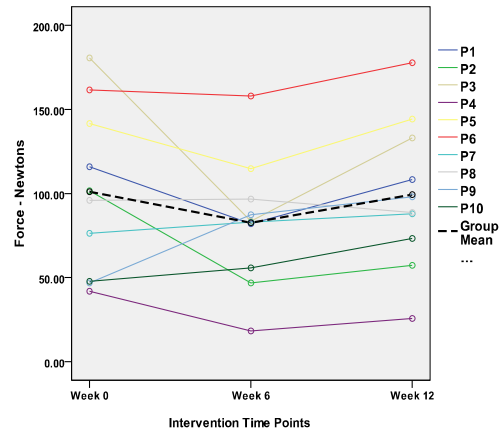


Figure 39 Plantar-Flexor Strength PRT Group

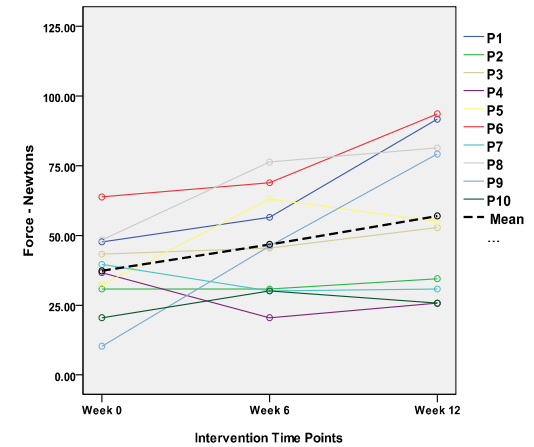


Figure 40 Gluteus Maximus Strength PRT Group

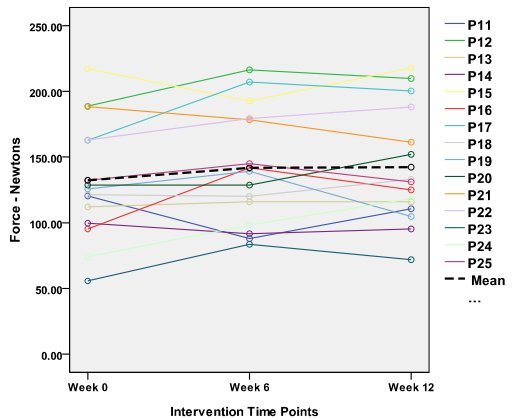


Figure 41 Quadriceps Strength KneeHab Group

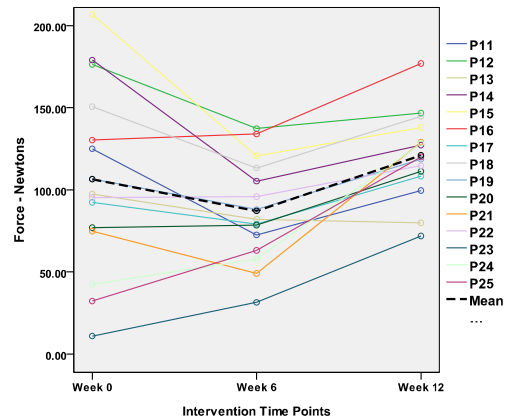


Figure 42 Plantar-Flexor Strength KneeHab Group

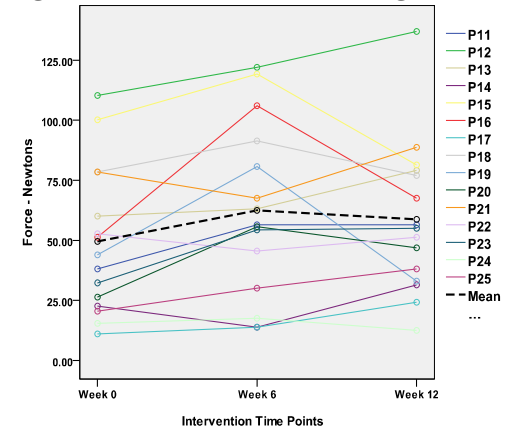


Figure 43 Gluteus Maximus Strength KneeHab Group

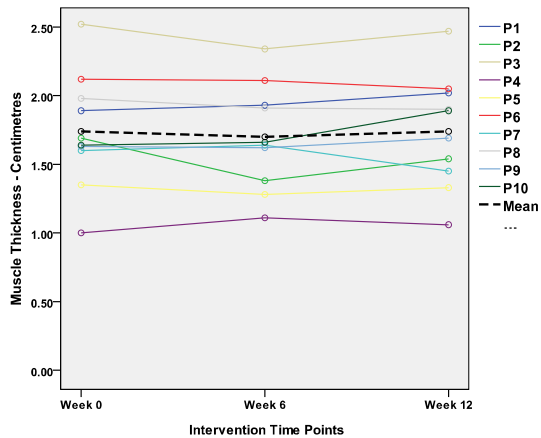


Figure 44 Rectus Femoris Thickness PRT Group

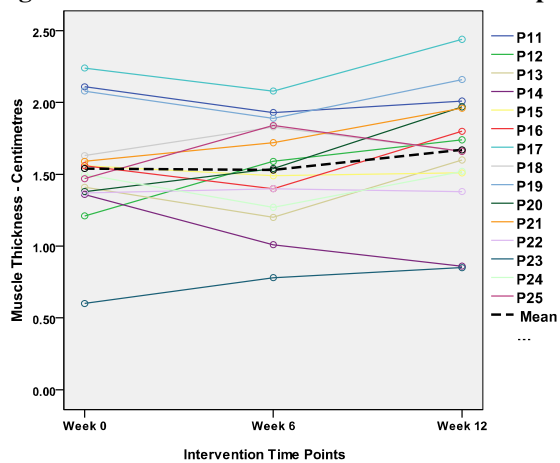


Figure 46 Rectus Femoris Thickness Kneehab Group

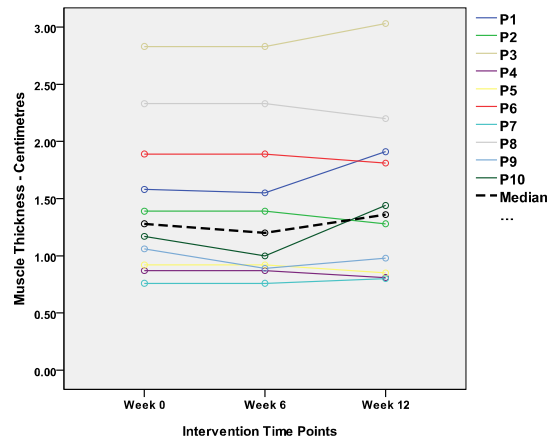


Figure 45 Vastus Intermedius Thickness PRT Group

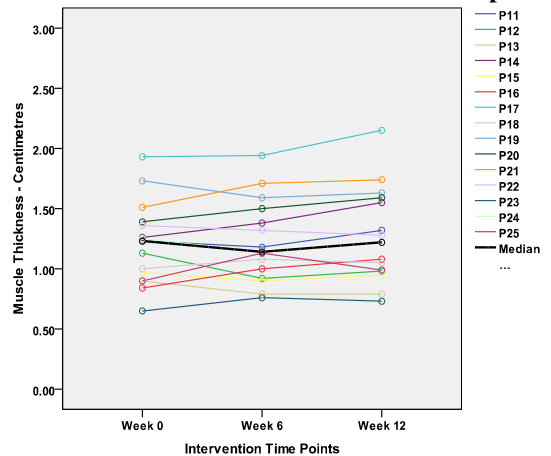


Figure 47 Vastus Intermedius Thickness Kneehab Group

Appendix 12 – Normalized Strength Data

Table 65 Descriptive Statistics and Within Group Treatment Effect for Quadriceps Strength (Newtons) - Impaired Side

	Median (Interquartile Range)			Friedman's ANOVA
Group	Week 0	Week 6	Week 12	p-value
PRT (n=10)	100 (0)	98.3 (47.1)	105.1 (49.9)	0.601
Kneehab (n=15)	100 (0)	109.6 (32.6)	109.6 (27.5)	0.374

Median (IQR): MFIS Cognitive Subscale Score

Table 66 Within Group Treatment Effect during Intervention Periods for Quadriceps Strength (Newtons) - Impaired Side

	Post-Hoc Analysis (Wilcoxon Signed-Ranks Test)					
	0-6 Weeks		6-12 Weeks		0-12 Weeks	
Group	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=10)	-1.8 (5 : 5 : 0)	0.922	7.8 (7 : 3 : 0)	0.195	5.1 (6 : 4 : 0)	0.322
Kneehab (n=15)	9.6 (9 : 5 : 1)	0.104	0 (7 : 7 : 1)	0.870	9.6 (5 : 10 : 0)	0.083

Ranks: Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (MFIS Cognitive Subscale Score).

Table 67 Between Group Treatment Effect for Quadriceps Strength (Newtons) - Impaired Side

Mann-Whitney U Test (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.461	0.338	0.935

Table 68 Descriptive Statistics and Within Group Treatment Effect for Plantar-Flexion Strength (Newtons) - Impaired Side

Group	Median (Interquartile Range)			Friedman's ANOVA
	Week 0	Week 6	Week 12	p-value
PRT (n=10)	100 (0)	89.3 (64.5)	97.7 (54.4)	0.135
Kneehab (n=15)	100 (0)	84.2 (37.1)	117.2 (90.5)	0.011*

Median (IQR): MFIS Cognitive Subscale Score; * : significant at p<0.05

Table 69 Within Group Treatment Effect during Intervention Periods for Plantar-Flexion Strength (Newtons) - Impaired Side

Group	Post-Hoc Analysis (Wilcoxon Signed-Ranks Test)					
	0-6 Weeks		6-12 Weeks		0-12 Weeks	
	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=10)	-10.7 (4 : 6 : 0)	0.375	19.3 (9 : 1 : 0)	0.006*	-2.40 (5 : 5 : 0)	0.922
Kneehab (n=15)	-15.8 (6 : 9 : 0)	0.421	28 (14 : 1 : 0)	<0.001**	17.2 (9 : 6 : 0)	0.124

*, **: significant at p<0.05, p<0.001 respectively; **Ranks:** Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change:** Change Score (MFIS Cognitive Subscale Score).

Table 70 Between Group Treatment Effect for Plantar-Flexion Strength (Newtons) - Impaired Side

Mann-Whitney U Test (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.643	0.160	0.261

Table 71 Descriptive Statistics and Within Group Treatment Effect for Gluteus Maximus Strength (Newtons) - Impaired Side

Group	Median (Interquartile Range)			Friedman's ANOVA
	Week 0	Week 6	Week 12	p-value
PRT (n=10)	100 (0)	113.3 (73.1)	135.9 (72.6)	0.032*
Kneehab (n=15)	100 (0)	122.9 (79.9)	131.6 (61.7)	0.087

Median (IQR): MFIS Cognitive Subscale Score; * : significant at p<0.05

Table 72 Within Group Treatment Effect during Intervention Periods for Gluteus Maximus Strength (Newtons) - Impaired Side

Post-Hoc Analysis (Wilcoxon Signed-Ranks Test)						
	0-6 Weeks		6-12 Weeks		0-12 Weeks	
Group	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value	Median of Change (Ranks)	p-value
PRT (n=10)	13.3 (7 : 2 : 1)	0.129	13 (8 : 2 : 0)	0.160	35.9 (8 : 2 : 0)	0.049*
Kneehab (n=15)	19.1 (12 : 3 : 0)	0.010*	2.3 (8 : 6 : 1)	0.987	31.4 (10 : 5 : 0)	0.018

* : significant at $p < 0.05$; **Ranks**: Number of participants whose score increased : decreased : was unchanged respectively; **Median of Change**: Change Score (MFIS Cognitive Subscale Score).

Table 73 Between Group Treatment Effect for Gluteus Maximus Strength (Newtons) - Impaired Side

Mann-Whitney U Test (p-value)		
0-6 Weeks	6-12 Weeks	0-12 Weeks
0.693	0.304	0.775

Appendix 13 – Participant Satisfaction Questionnaire

Items	Definitely Agree	Generally Agree	Neither Agree nor Disagree	Generally Disagree	Definitely Disagree
1. The Kneehab device was easy to put on and take off	1	2	3	4	5
2. The controller for the Kneehab device was easy to use	1	2	3	4	5
3. The feeling of stimulation from the Kneehab was comfortable	1	2	3	4	5
4. The Kneehab device was easy to use with the exercises	1	2	3	4	5
5. I feel I benefitted from using the Kneehab device	1	2	3	4	5
6. Having the Kneehab device encouraged me to do my exercises	1	2	3	4	5

Additional Comments:

Appendix 14 – List of Original Presentations

The following presentations have arisen from the studies detailed in this thesis:

- Hughes, L., Donnelly, A., Rainsford, G., Minogue, C. and Coote, S. (2010) ‘The Functional and Physiological Correlates of Quadriceps Muscle Power and Endurance in People with Multiple Sclerosis’, Irish Society of Chartered Physiotherapists Annual Conference (Poster Presentation), Limerick, November 2010.
- Hughes, L., Donnelly, A., Rainsford, G., Minogue, C. and Coote, S. (2011) ‘Augmenting Progressive Resistance Training with Neuromuscular Electrical Stimulation in People with Multiple Sclerosis’, 2nd Annual Conference of the International Functional Electrical Stimulation Society (Oral Presentation), Dublin, March 2011.
- Hughes, L., Donnelly, A., Rainsford, G., Minogue, C. and Coote, S. (2011) ‘Augmenting Progressive Resistance Training with the Kneehab Device – Programme Adherence and Usability of the Device’, accepted to the 16th Annual Rehabilitation in Multiple Sclerosis Conference (Poster Presentation), Turku, May 2011.
- Hughes, L., Donnelly, A., Rainsford, G., Minogue, C. and Coote, S. (2011) ‘The Effects of Progressive Resistance Training Augmented with Neuromuscular Electrical Stimulation on Fatigue and Mobility’, accepted to the 16th Annual Rehabilitation in Multiple Sclerosis Conference (Poster Presentation), Turku, May 2011.
- Hughes, L., Donnelly, A., Rainsford, G., Minogue, C. and Coote, S. (2011) ‘Augmenting an Exercise Programme with Neuromuscular Electrical Stimulation for People with Multiple Sclerosis – The Effect on Strength and Fatigue’, accepted to the World Confederation of Physical Therapy Conference (Poster Presentation), Amsterdam, June 2011.

- Hughes, L., Donnelly, A., Rainsford, G., Minogue, C. and Coote, S. (2011) 'The Clinical Outcomes of Augmenting an Exercise Programme with Neuromuscular Electrical Stimulation in People with Multiple Sclerosis', accepted to the World Confederation of Physical Therapy Conference (Poster Presentation), Amsterdam, June 2011.

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